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SYNTHESIS OF
3-(((P-NITROPHENYL) SULFONYL)
OXY) 2-KETO ESTERS FROM
ALPHA-KETO ESTERS AND A
SURVEY OF THEIR REACTIONS AS
1,2,3-TRIFUNCTIONALIZED
INTERMEDIATES

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FROM α -KETO ESTERS AND A SURVEY OF THEIR REACTIONS AS
1,2,3-TRIFUNCTIONALIZED INTERMEDIATES

BY
MARY CATHERINE JOHNSON, B.S.

A Dissertation submitted to the Graduate School
in partial fulfillment of the requirements
for the Degree
Doctor of Philosophy

Major Subject: Chemistry

New Mexico State University
Las Cruces, New Mexico
July 1996

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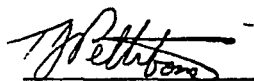
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"Synthesis of 3-[[[*p*-Nitrophenyl]Sulfonyl]Oxy] 2-Keto Esters from α -Keto Esters and a Survey of their Reactions as 1,2,3-Trifunctionalized Intermediates," a dissertation prepared by Mary Catherine Johnson in partial fulfillment of the requirements for the degree, Doctor of Philosophy, has been approved and accepted by the following:



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This work is dedicated to my parents, Harry and Marilyn Johnson, my brother Michael Johnson, and my friends for the love and encouragement they have given me.

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ABSTRACT

SYNTHESIS OF 3-[[(*p*-NITROPHENYL)SULFONYL]OXY] 2-KETO ESTERS
FROM α -KETO ESTERS AND A SURVEY OF THEIR REACTIONS AS
1,2,3-TRIFUNCTIONALIZED INTERMEDIATES

BY

MARY CATHERINE JOHNSON, B.S.

Doctor of Philosophy in Chemistry

New Mexico State University

Las Cruces, New Mexico, 1996

Dr. Robert V. Hoffman, Chair

3-[[(*p*-Nitrophenyl)sulfonyl]oxy] 2-keto esters, **15**, were efficiently prepared in good yields by electrophilic attack of *bis*(*p*-nitrobenzenesulfonyl)-peroxide (*p*-NBSP) on the electron-rich carbon-carbon double bond of 1-carboethoxy-1-(trimethylsiloxy)-alkenes, **11**. Silyl enol ethers **11** were prepared from α -keto esters in good to excellent yields by two methods that differed by the base used to remove the proton.

Carbonyl reactions and substitution reactions of **15** were investigated. The carbonyl of **15** was found to be very electrophilic, as demonstrated by the facile reaction of **15** with water to provide *gem*-diols **16**. The mild reducing

agent, sodium triacetoxyborohydride easily reduced **15** to give *syn*-3-[(*p*-nitrophenyl)sulfonyloxy]-2-hydroxy esters, **18** in good yields. The Felkin-Anh model was used to rationalize the stereoselectivity of the reduction reaction. Base-promoted, stereoselective ring closure of **18** provided *cis*-glycidic esters, **cis-22**, in good yields.

Reactions of **15** with nucleophilic amines gave base-promoted decomposition. Due to the high reactivity of **15**, the scope of the survey of reactions was limited to the reactions of **15b**. Nucleophiles with a low pK_a , such as morpholine and azide ion, replaced the nosylate group of **15b** to afford ethyl 3-morpholino-2-oxo-4-phenyl butanoate, **24**, and ethyl 3-azido-2-oxo-4-phenylbutanoate, **30b**, in good yields. Two sequences: reduction-protection-substitution, RPS, and substitution-reduction-protection, SRP, of **30b** were evaluated. Both sequences provided ethyl 3-azido-2-carboethoxy-4-phenylbutanoate, **34b**. While more diastereoselective, the RPS sequence gave only modest yields of *anti*-**34b**, due to competing elimination reactions. Better yields were obtained for the SRP sequence.

Condensation reactions of **15b** with acetamide and methyl carbamate provided an efficient route to oxazoles **42** and oxazolones **40**. The mechanism of the oxazole reaction was investigated to confirm the structural assignment of **42**. Intermediate, 2-methyl-2-hydroxy-4-carboethoxy-5-benzyl-3-oxazoline, **46**, was isolated. The structure of **42** was further substantiated by the acid-catalyzed oxazole ring-cleavage of **42** to provide ethyl 2-acetamido-3-oxo-4-phenylbutanoate, **53**.

TABLE OF CONTENTS

LIST OF TABLES	ix
LIST OF FIGURES	x

Chapter

1. INTRODUCTION	1
2. SYNTHETIC APPROACHES TO 1,2,3-TRIFUNCTIONALIZED COMPOUNDS	11
3. RESEARCH OBJECTIVES	48
4. RESULTS	50
4.1 Preparation of 3-[[(<i>p</i> -Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters	50
4.2 Reactions of 3-[[(<i>p</i> -Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters	70
5. DISCUSSION	104
5.1 Preparation of 3-[[(<i>p</i> -Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters	104
5.2 Reactions of 3-[[(<i>p</i> -Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters	118
6. CONCLUSIONS	161
7. EXPERIMENTAL SECTION	163
REFERENCES CITED	202

LIST OF TABLES

TABLE 1. Availability of α -Keto Esters	51
TABLE 2. Preparation of Silyl Enol Ethers using Triethylamine	55
TABLE 3. Preparation of Silyl Enol Ethers of 1-Phenyl-2-Propanone	56
TABLE 4. Preparation of Silyl Enol Ethers using Potassium Hydride	58
TABLE 5. Preparation of 3-[[(<i>p</i> -Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters ...	64
TABLE 6. Percent Hydration of 3-[[(<i>p</i> -Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters	67
TABLE 7. Hydration of 3-[[(<i>p</i> -Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters in Acetone- <i>d</i> ₆	69
TABLE 8. Reduction of 3-[[(<i>p</i> -Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters with Sodium Borohydride	73
TABLE 9. Reduction of 3-[[(<i>p</i> -Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters with Sodium Triacetoxyborohydride	75
TABLE 10. Protection of 18b and 18d with Acetyl Chloride	77
TABLE 11. Ring Closure of 18b and 18c	78

LIST OF FIGURES

FIGURE 1. 1,2,3-Trifunctionalized Fragment	1
FIGURE 2. Different Oxidation Levels for α,β -Disubstituted Carboxylic Acid Derivatives	3
FIGURE 3. Common Structural Types of α,β -Disubstituted Carboxylic Acid Derivatives	4
FIGURE 4. Different Synthetic Strategies to α,β -Disubstituted Carboxylic Acid Derivatives	13
FIGURE 5. Possible Differential Reactivity Structures	36
FIGURE 6. Possible NOE Enhancements for E-11b and Z-11b	61
FIGURE 7. General Types of Carbonyl Chemistry	71
FIGURE 8. Reduction-Substitution and Substitution-Reduction	72
FIGURE 9. NOE Enhancements of cis-22b and cis-22c	80
FIGURE 10. Revised Reduction and Substitution Schemes	90
FIGURE 11. Conformations Leading to <i>cis</i> and <i>trans</i> Enolates of 10b,c	110
FIGURE 12. Newman Projections of Conformation A and Conformation B	111
FIGURE 13. Complexation of <i>p</i> -NBSP with Zn^{+2}	114
FIGURE 14. Cram's Open Chain Model for Asymmetric Induction	130
FIGURE 15. Possible Felkin-Anh Conformers for Reduction of 15b,c	131
FIGURE 16. Favorable Felkin-Anh Conformers for Reduction of 15b-d	132
FIGURE 17. Possible Felkin-Anh Conformers for Reduction of 30b	139
FIGURE 18. Favorable Felkin-Anh Conformers for Reduction of 30b	140
FIGURE 19. Summary of Azide Substitution and Reduction Sequences	145
FIGURE 20. General Structure for 4-oxazolin-2-one	150
FIGURE 21. General Structure for 1,3-oxazole	151

1. INTRODUCTION

The development of methodology for the synthesis of 1,2,3-trifunctionalized compounds has received a great deal of attention recently. 1,2,3-Trifunctionalized compounds are of interest because the 1,2,3-trifunctional array is a structural component found in many biologically active natural products. For many of these natural products, it is the 1,2,3-trifunctionalized component that provides the biological activity of the compound. A 1,2,3-trifunctionalized fragment is characterized as having three adjacent, functionalized carbons on a carbon chain (Figure 1). The three carbons can be at the same or different oxidation levels, but each carbon is attached to a hetero atom containing functional group, E, Y, or Z.

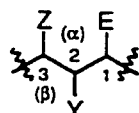


Figure 1. 1,2,3-Trifunctionalized Fragment

Three oxidation levels are possible for each of the three carbons. For example, if the hetero atom is an oxygen, then the three different oxidation levels possible at that carbon are carboxylic acid, ketone, or alcohol. Likewise, each of the other carbons of the 1,2,3-trifunctionalized array could be part of different functional groups or the same functional groups depending on the hetero atom and the oxidation level at that carbon.

As can be imagined, there are a wide variety of compounds that fit these definitions, so to make the discussion manageable, some structural conditions will be assumed. First, the C_1 will be limited to carboxylic acid derivatives, since many biologically important 1,2,3-trifunctionalized fragments are carboxylic acid derivatives. Since the 1,2,3-trifunctional array is usually found at the end of a carbon chain, IUPAC rules dictate that 1,2,3-trifunctionalized molecules be named as 2,3-disubstituted acid derivatives. However, it is customary to use the Greek letters α and β to denote the position 1 and 2 from the terminal functional group. This custom will be followed here since most people clearly recognize an α -amino acid as a 2-amino acid and a β -keto ester as a 3-oxoester.

As a second simplification, the functional groups Y and Z will be either the ketone or alcohol oxidation levels. Within these specifications, there are three common combinations of oxidation levels for α,β -disubstituted carboxylic acid derivatives (Figure 2). For oxidation level I, both Y and Z exist in the ketone oxidation state, and this combination has the highest overall oxidation level. The next highest oxidation level, oxidation level II, is that in which either Y or Z exists in the ketone oxidation state and the other group is found in the lower, alcohol oxidation state. In the lowest combined oxidation level, oxidation level III, both Y and Z exist at the alcohol oxidation state. Theoretically, a higher combined oxidation level can be accessed from a lower combined oxidation level by oxidation, and a lower combined oxidation level may be reached from a higher combined oxidation level by a reduction.

A third structural consideration of α,β -disubstituted carboxylic acid derivatives is the nature of the functional groups Y and Z. The most common

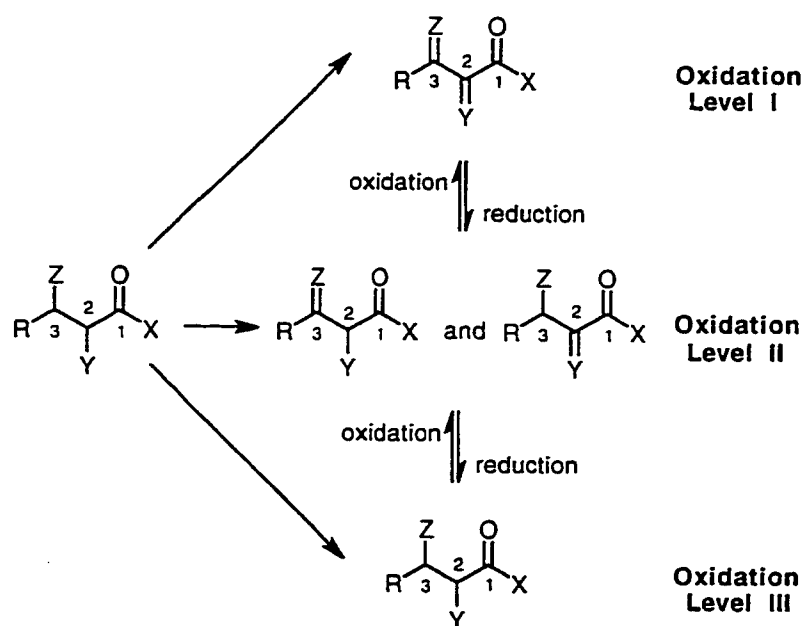


Figure 2. Different Oxidation Levels for α,β -Disubstituted Carboxylic Acid Derivatives

and dominant functional groups in organic chemistry contain oxygen and nitrogen,¹ so Y and Z will be further limited to functional groups containing oxygen and nitrogen. With these limitations on the C₁ group (carboxylic acid group) and the nature of Y and Z (oxygen and nitrogen), there are eleven common structural types of α,β -disubstituted carboxylic acid derivatives at the three basic oxidation levels (Figure 3).

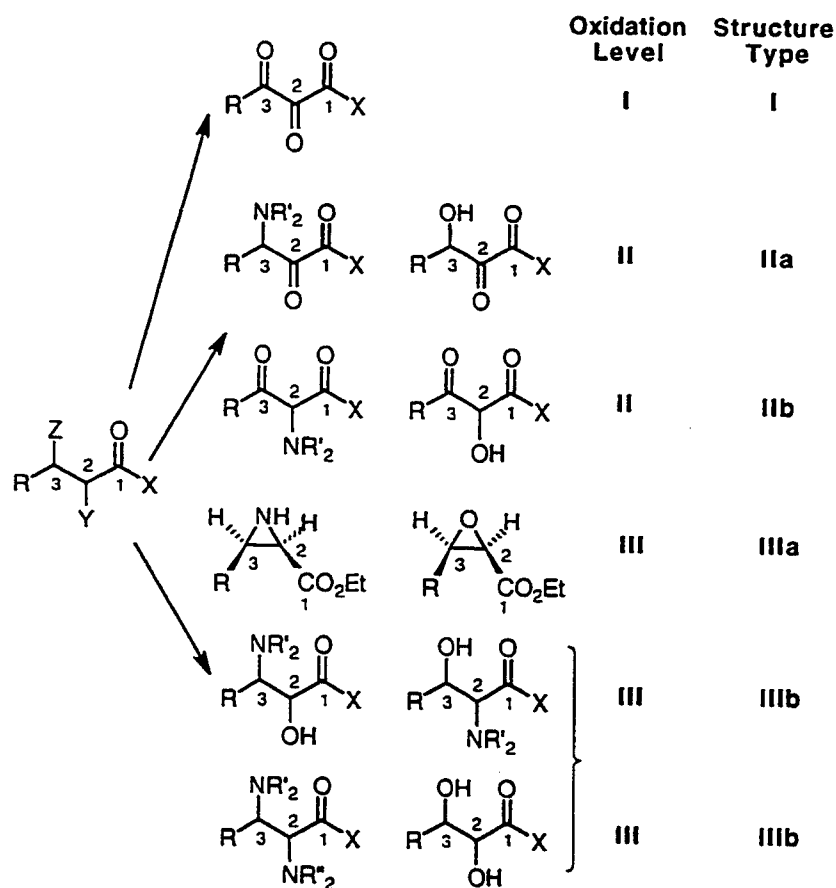


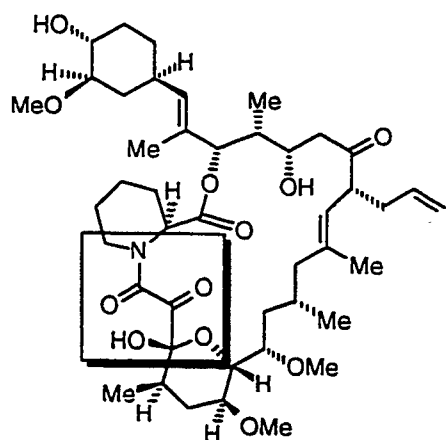
Figure 3. Common Structural Types of α,β -Disubstituted Carboxylic Acid Derivatives

For oxidation level I, there is essentially only one known structural type and that is the α,β -diketo ester or α,β -diketo amide (also called a 1,2,3-tricarbonyl compound). For this structure, both of the hetero atoms Y and Z are oxygens. The second oxidation level, oxidation level II, has two isomeric

structures possible with the ketone oxidation state at the α -carbon in structure IIa and at the β -carbon in structure IIb. Consequently, structure IIa type describes β -amino- α -keto esters and β -hydroxy- α -ketoesters, and structure IIb consists of β -oxo- α -amino esters and β -oxo- α -hydroxy esters. The lowest combined oxidation level, oxidation level III, consists of two basic structures. Structure IIIa consists of the small ring compounds the α,β -aziridiny esters and the α,β -glycidic esters where Y and Z bridge C₂ and C₃ and are the same atom. The last structure, structure IIIb is the largest category, and it consists of the four different combinations of oxygen and nitrogen at the α and β positions. These structures are the α,β -diamino ester, α,β -dihydroxy ester, β -amino- α -hydroxy ester, β -hydroxy- α -amino ester. Clearly, there are many classes of compounds that fit the general definition of a 1,2,3-trifunctionalized compound that are not represented here, but the structures shown (Figure 3) are ones that are commonly found in nature and in many biologically interesting compounds.

The need for novel procedures to access 1,2,3-trifunctionalized compounds is underscored by their occurrence in a wide variety of important drugs and natural products. One example of a biologically active tricarbonyl compound (Oxidation level I, Figure 3) is FK-506, I-1.² FK-506 is a potent immuno-suppressant, and it has superior potency to cyclosporin A,^{3,4} a drug currently used to inhibit the responses to allograft transplantation. FK-506 is a 23-membered macrolide lactone, and the 1,2,3-trifunctionalized fragment it contains is a hemiketal-masked α,β -diketo amide functionality (a 1,2,3-tricarbonyl amide). The α,β,γ -tricarbonyl system is a potent electrophile, and has been found essential for the biological activity of FK-506.⁵ Other

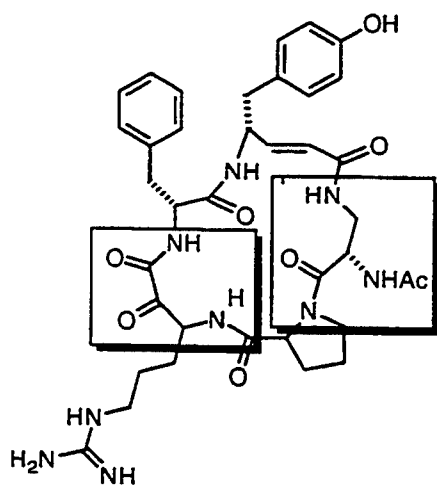
biologically interesting compounds containing the 1,2,3-tricarbonyl functional array include the antifungal antibiotic rapamycin^{6,7} and the structurally similar antibiotic demethoxyrapamycin.⁸



I-1
FK-506

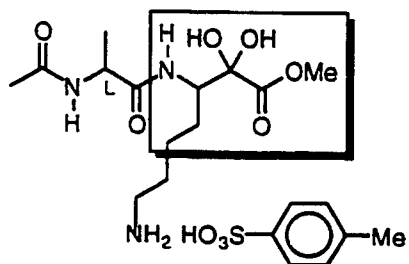
As an example of a biologically active compound with the mixed combined oxidation state (Oxidation level II, Structure Type IIa, Figure 3), cyclotheonamide B, I-2, was recently isolated as a secondary metabolite from marine sponges, and it was found to be a potent and selective inhibitor of the serine protease thrombin.⁹ The unique β -amino- α -keto amide fragment as well as an α,β -diamino amide fragment (Oxidation level III, Structure Type IIIb, Figure 3) are found in the cyclopentapeptide structure. Although there are not many natural products found with this functional grouping, there has

been a recent surge of interest for the synthesis of the β -amino- α -keto ester^{10,11} and amide¹² component(s) for use as inhibitors of cysteine, serine,



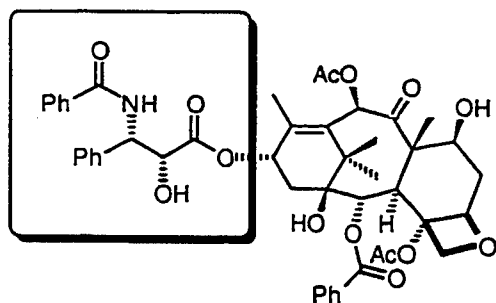
I-2
cyclotheonamide B

and aspartyl proteinases. The peptide mimetic, **I-3**, was recently synthesized and found to be a potent trypsin inhibitor. It contains a β -amino- α -keto ester, masked as the hydrated *gem* diol form.¹³



I-3

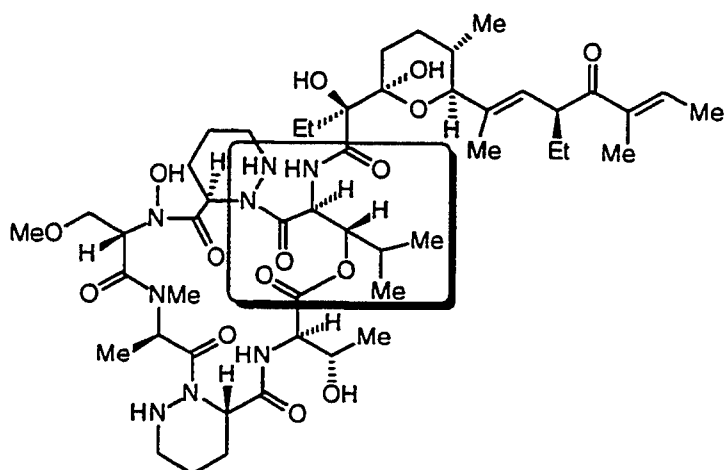
There are a greater number of naturally occurring compounds which have the hydroxyl and amine functions at C₂ and/or C₃ (Oxidation level III, Structure IIIb, Figure 3). The most common examples are the β -hydroxy- α -amino acids serine and threonine. Another compound, which contains a β -hydroxy- α -amino acid unit and has captured the nation's attention, is taxol.



I-4
taxol

Taxol, I-4, is a diterpene of the taxane group that has been isolated from several species of the *Taxus* genus, and it has been found to exhibit potent antileukemic and antitumor inhibitory properties.¹⁴ The β -amino- α -hydroxyamide unit is found on the C₁₃ side chain of taxol and is required for antitumor activity.^{15,16} Other biological examples in this group are the antibiotics azinotricin, I-5,¹⁷ and telomycin¹⁸ which both contain an unusual *erythro*- β -hydroxyleucine moiety.

In the previous biologically significant examples, a wide variety of molecular structures and 1,2,3-trifunctionalized arrays can be seen. For many of the 1,2,3-trifunctionalized compounds, such as FK-506⁵ and taxol,¹⁵



**I-5
azinothricin**

the 1,2,3-trifunctionalized fragment is often found to be essential to the biological activity of compound. Therefore, 1,2,3-trifunctionalized component is considered to be part of the pharmacophore.¹⁹ Since the different types of interactions that each of the biologically active 1,2,3-trifunctionalized containing compounds has with each specific receptor will be unique, it would be difficult to make a generalized statement as to the structure reactivity relationship of the 1,2,3-trifunctionalized moiety to a receptor.

However the 1,2,3-trifunctionalized fragment interacts with the receptor, these interactions will be governed by the same secondary bonding forces that influence all interacting organic molecules. Some of these secondary bonding forces are covalent bonding, ionic interactions, ion-dipole and dipole-dipole interactions, hydrogen bonding, hydrophobic interactions

and van der Waals interactions.¹⁹ The increased number of hetero atom containing functional groups in a small area, as is the case for 1,2,3-trifunctionalized molecules, must provide more opportunities for these type of interactions to occur, and consequently, the 1,2,3-trifunctionalized component is integral for the bioactivity. For these reasons, great interest in the synthesis of 1,2,3-trifunctionalized compounds has been fostered, and many different approaches to specific 1,2,3-trifunctionalized arrays have been developed. However, no versatile synthetic method has been developed for all the functional group arrays.

2. SYNTHETIC APPROACHES TO 1,2,3-TRIFUNCTIONALIZED COMPOUNDS

Many factors contribute to the molecular complexity²⁰ of each of the unique 1,2,3-trifunctionalized arrays. In general, the high functional group density and the high chemical reactivity of the densely functionalized fragment coupled with stereochemistry requirements lead to the main sources of the molecular complexity of 1,2,3-trifunctionalized molecules. In such compounds, there are three potential sites of reactivity, and these sites of reactivity are further influenced by the adjacent functional groups.

Transformations of adjacent functional groups, may by their proximity, cause subsequent, intramolecular reactions. Oftentimes, reliable standard reactions and reagents for functional group transformations may fail in the polyfunctional environment,²⁰ and it is difficult to predict when this unusual reactivity may occur. Therefore, optimum conditions for the preparation of 1,2,3-trifunctionalized compounds take considerable time and effort to discover, and the order of the steps in a multi-step, synthetic sequence has to be carefully planned so subsequent steps don't interfere with existing functionality.

For example, electrophilic sites by their proximity to other electron withdrawing groups, are made more electrophilic. In tricarbonyl compounds (Oxidation level I, Figure 3), the tricarbonyl array can act as a di- or tri-electrophile in a single reaction. This multifunctionality has been masterfully used by Wassermann for the preparation of isoquinoline alkaloids.²¹ In compounds in the two lower combined oxidation states (Structure II and

Structure III, Figure 3), the oxygen and the nitrogen can act as nucleophiles, and the carbonyl groups can act as electrophiles. The combination of a nucleophilic and an electrophilic site in one molecule tends to cause self-condensation or oligomerization.

The complexity posed by the high functional group content of multifunctional 1,2,3-trifunctionalized compounds is the biggest obstacle in the synthesis of these compounds, and many methods for the preparation of these compounds only address this problem. However, the chirality of the 1,2,3-trifunctionalized component can also pose problems. Only carbons at the lowest oxidation state (alcohol level) will have potential chirality considerations, so no chirality restrictions for 1,2,3-tricarbonyl arrays (Oxidation level I, Figure 3) exist. For structures at the middle combined oxidation state (Structure IIa and Structure IIb, Figure 3), only the chirality of one C₂ or C₃ must be considered. Compounds with the lowest combination of oxidation levels (Structure IIIa and Structure IIIb, Figure 3), have two chiral centers, and consequently, the complexity of the synthesis is significantly increased. In all cases, additional chirality in the rest of the molecule can contribute to the molecular complexity, so chirality must be selectively installed with proper timing so that epimerization of existing chiral centers of the 1,2,3-trifunctional array and other chiral centers in the rest of the molecule can be avoided.

There are several different approaches (Figure 4) to the construction of the molecular skeleton of the 1,2,3-trifunctionalized component, and a few of these will be described. The first strategy, Strategy A (Figure 4), constructs the molecular backbone by the addition of functional group E to the Y-Z

fragment, so the bond formed is between the C₁ and C₂ of the 1,2,3-trifunctional array. A similar idea is shown in Strategy B (Figure 4) where the bond formed is between the C₂ and C₃ by the addition of functional group Z to the Y-E fragment. Strategy C (Figure 4) consists of stereoselective, difunctional group addition at C₂ and C₃, and Strategy D (Figure 4) involves the oxidative alkylation of the α-carbon. Although not shown, a similar

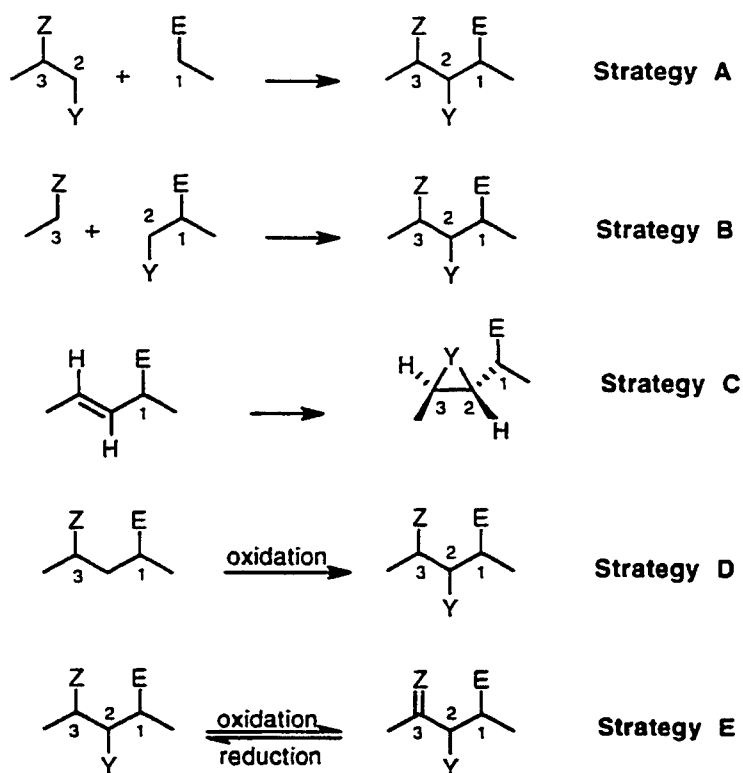


Figure 4. Different Synthetic Strategies to α,β -Disubstituted Carboxylic Acid Derivatives

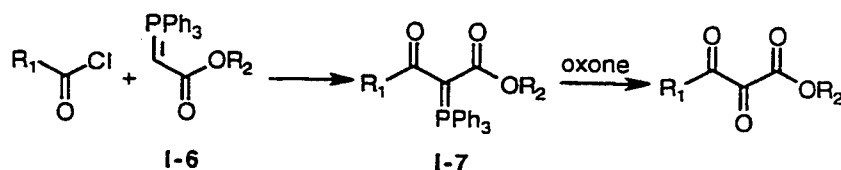
approach includes the oxidative alkylation at the β -carbon of an α -keto carboxylic acid derivative. Strategy E (Figure 4) is the simplest of these synthetic strategies and consists of functional group transformation of existing functional groups by oxidation and reduction techniques. Those transformations that form carbon-carbon bonds as in Strategy A and B are usually considered as being more significant than functional group transformations.²⁰ Also important are those reactions that generate stereocenters as in Strategy C and those that provide new functional groups, Strategy D.

Even though the high functional group density and consequently high chemical reactivity are major factors complicating the preparations of 1,2,3-trifunctionalized compounds, the synthesis of these compounds share the same goals of efficiency and chemoselectivity as any other chemical strategy. Ideally, there should be minimal functional group interferences in subsequent reaction steps, and the overall synthesis should require the fewest number of steps possible. With the strategies and goals enumerated, it is instructive to examine some examples of the preparation of 1,2,3-trifunctionalized arrays in which these strategies have been reduced to practice. The discussion will be loosely grouped around the three different combined oxidation states, and while many different strategies have been utilized, only some of the more representative examples will be discussed.

The tricarbonyl array can be constructed in a two step reaction sequence by the reaction of an acylphosphoranylidene, **I-6**, with acyl chlorides (Equation 1) in the presence of *bis*(trimethylsilyl)acetamide to form a keto ylide carboxylate, **I-7**. Oxidative cleavage of **I-7** by potassium

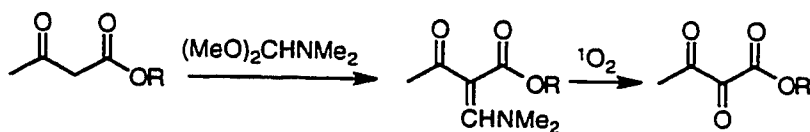
peroxymonosulfate (Oxone) provides the 1,2,3-tricarbonyl compound.^{4,22,23}

This general approach represents a carbon-carbon bond forming process (Strategy B, Figure 4).



Equation 1

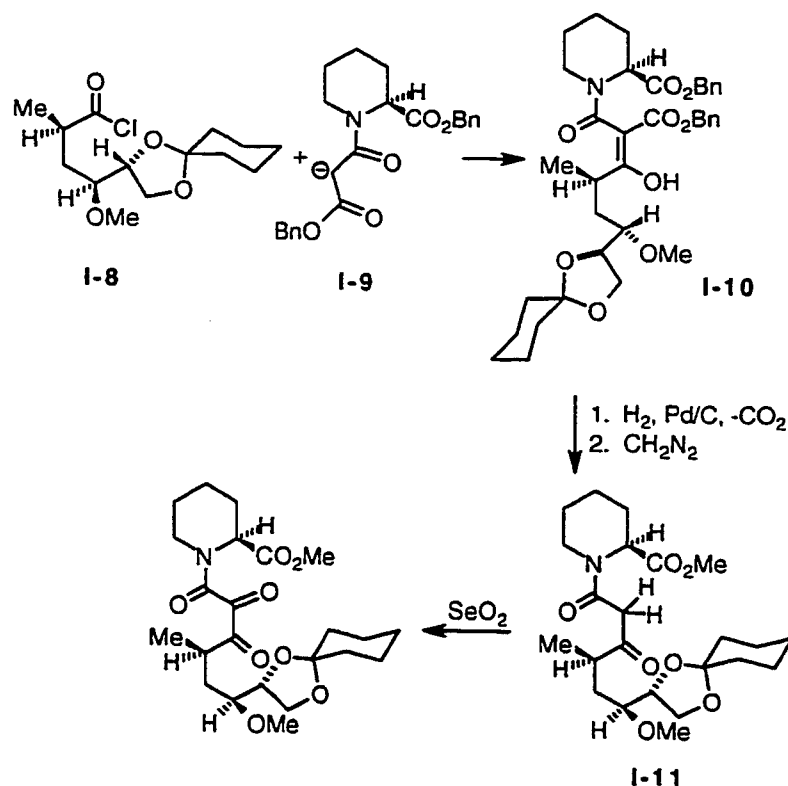
The tricarbonyl array can also be synthesized (Equation 2) by the reaction of β -keto esters with the dimethylformamide dimethylacetal to provide an intermediate enamine followed by photooxidative cleavage of the intermediate enamine.²⁴ Again, this is a general synthesis of target molecules that have no stereocenters (Strategy D, Figure 4).



Equation 2

Another malonic ester type synthesis used for the synthesis of FK-506 (Equation 3) incorporates the appropriate chirality of the backbone before installation of the α,β -diketo amide (Strategy D, Figure 4). In the first step, the enolate of a malonic ester, **I-9**, was acylated by addition of acyl chloride, **I-8** to give **I-10**.⁵ Hydrogenation of **I-10** removed the benzyl protecting groups and

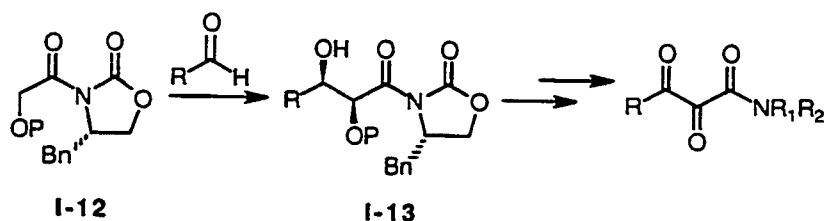
concomitant decarboxylation of the β -keto acid group ensued. Diazotization provided the methyl ester, **1-11**, and finally the central ketone was installed by oxidation with selenium dioxide of the α -carbon.



Equation 3

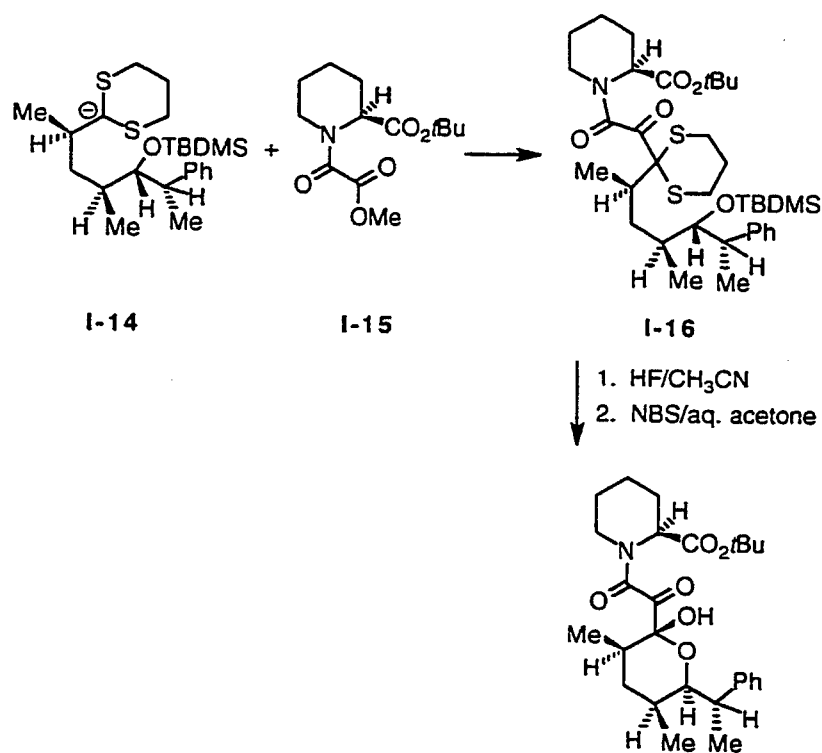
A particularly interesting synthesis of FK-506 (Equation 4) utilizes an asymmetric oxazolidinone aldol approach.³ In this preparation, a protected α -hydroxy imide, **1-12**, is added to an aldehyde to provide the α,β -dihydroxy

ester, **I-13** (Strategy B, Figure 4). Deprotection and oxidation provided the tricarbonyl unit. Since the two generated chiral centers are lost by oxidation, this example could be considered a case of overengineering. The mild conditions of the boron aldol methodology were more suitable for the base and acid sensitive multifunctional backbone of the precursor. Although this provided a direct route to **I-13**, the order of the deprotection and oxidation steps as well as the nature of the protecting groups caused the preparation of the α,β -diketo amide to be circuitous. Only after many attempts at different protection/deprotection schemes and oxidation of the α,β -dihydroxy ester by *bis*-oxidation utilizing the Swern method was the α,β -diketo amide obtained.



Equation 4

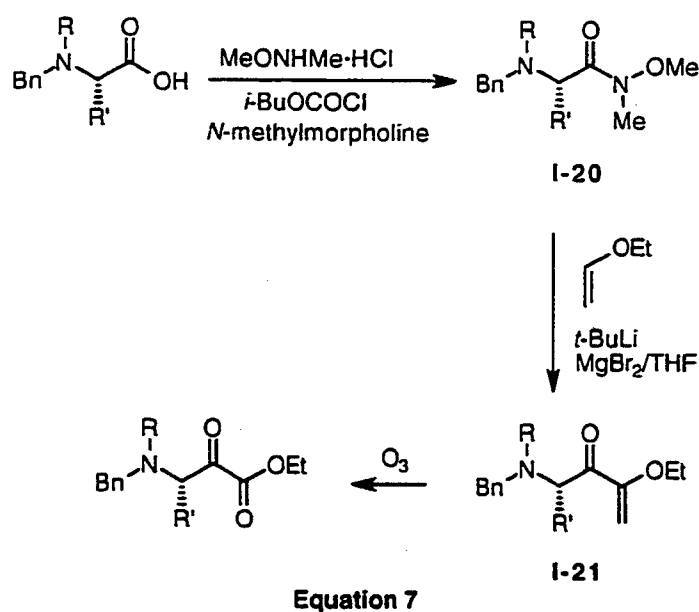
Another procedure for the preparation of the tricarbonyl amide of FK-506 utilizes the addition of a lithiodithiane, **I-14**, to an α -carbomethoxy amide, **I-15**, to give a β -dithionyl- α -keto amide, **I-16** (Equation 5).^{25,26} Deprotection of the OTBS group, cleavage of the dithiane by reaction with NBS, *N*-bromosuccinimide, followed by intramolecular cyclization provides the tricarbonyl compound. This procedure installs the 1,2,3-trifunctionalized component late in the sequence with no epimerization of any of the stereocenters (Strategy B, Figure 4).



Equation 5

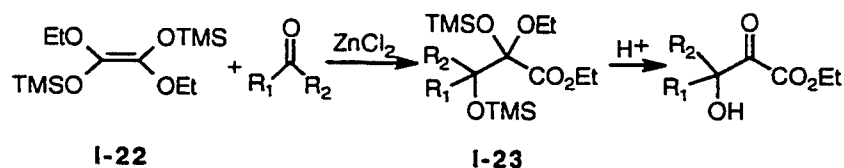
As can be seen by the examples, several different strategies can be used for the preparation of tricarboxyl compounds (Strategy B and D, Figure 4). In all cases, however, late installation of the tricarboxyl group is necessary due to the inherently high reactivity of this group. The center carbonyl group is the most electrophilic due to the activation by two adjacent carbonyl groups.^{21,27,28} Very few transformations of this higher oxidation state to either of the lower combined 1,2,3-trifunctionalized arrays have been

the chirality of α -amino acids. The α -amino acids are transformed into the *N*-methyl-*N*-methoxy carboxamides, **I-20**, and **I-20** is converted into an α -keto vinyl ether functionality by treatment with lithiated ethyl vinyl ether to afford the ethoxyvinyl ketones, **I-21** (Equation 7).^{10,11} Ozonolysis of **I-21** provides the desired β -amino- α -keto ester. While the chirality of the C₃ of **I-20** is determined by the choice of the α -amino acid, the versatility of the synthesis is also limited by the availability of the α -amino acid. Oxidation of β -amino- α -hydroxyesters by Swern or Dess-Martin oxidation provides an alternative route to β -amino- α -ketoesters (Strategy E, Figure 4).^{12,30}



The β -hydroxy- α -ketoester structure can be prepared by the addition of 1,2-diethoxy-1,2-disilyloxyethylene, **I-22**, with ketones in the presence of

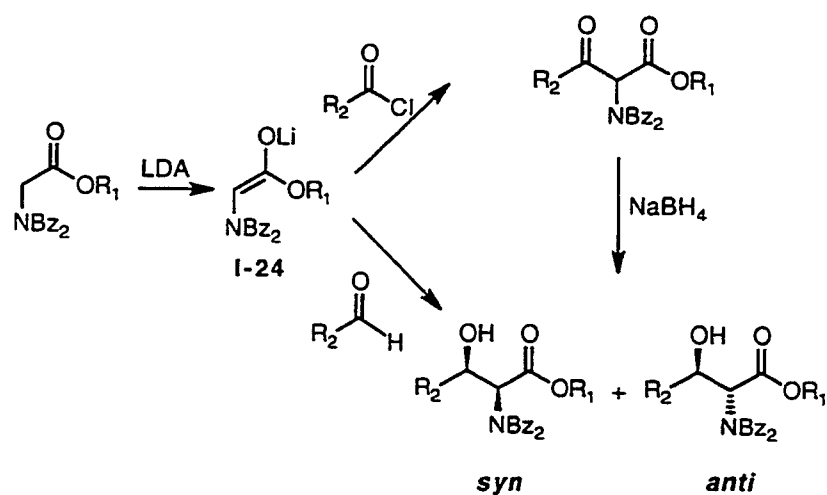
Lewis acids to give **I-23** (Equation 8).³¹ Hydrolysis of **I-23** provides the β -hydroxy- α -keto ester. The requisite **I-22** is prepared from diethyl oxalate by treatment with sodium/potassium and trimethylsilyl chloride. This general synthesis reverses the polarity of the normally electrophilic diethyl oxalate (Strategy B, Figure 4). As can be seen from examination of the literature, there are not many methods reported for the synthesis of either β -hydroxy- α -ketoesters or β -amino- α -ketoesters due to the difficulty in synthesizing molecules with both an active electrophilic and nucleophilic site.



Equation 8

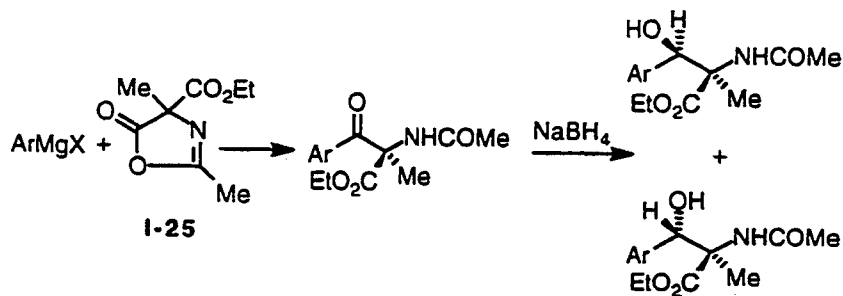
In contrast to β -substituted- α -keto esters (Structure IIa, Figure 3), there are a number of routes to β -keto- α -amino esters (Structure IIb, Figure 3). Although the procedure does not provide any stereochemical control, this structure is readily prepared (Strategy B, Figure 4) by the condensation of lithium enolates of *N*-protected glycines, **I-24**, with acyl chlorides to afford the β -oxo- α -amino esters (Equation 9).^{32,33} Treatment of the same enolate, **I-24**, with an aldehyde affords β -hydroxy- α -amino esters (Structure IIIb, Figure 3), although the diastereoselectivity is only moderate. Reduction of the β -oxo- α -amino ester also provides the β -hydroxy- α -amino esters (Strategy E, Figure 4). Interestingly, the two-step acylation and reduction provides better

stereoselectivity for the preparation of β -hydroxy- α -amino esters than the one-step aldol reaction does. Another older method for the preparation of



Equation 9

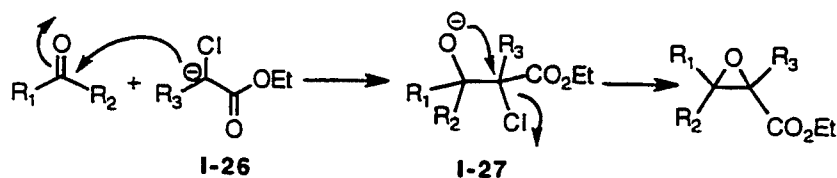
β -keto- α -amino esters utilizes α -amino- β -diesters, masked as oxazolones, I-25, and alkylation of I-25 by Grignard reagents at C_3 provides



Equation 10

β -oxo- α -acetamido esters (Equation 10).³⁴ As in the previous example (Equation 9), reduction of β -oxo- α -acetamido esters with sodium borohydride affords β -hydroxy- α -acetamido esters (Strategy E, Figure 4).

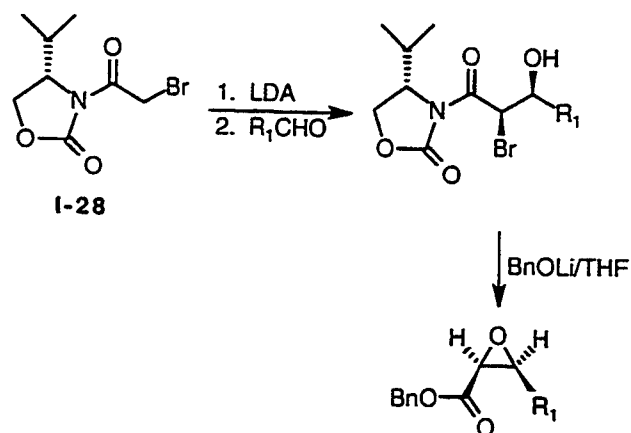
The first category of molecules having structure III consists of the α,β -oxirane esters (hetero atom is oxygen) and the α,β -aziridinyl esters (hetero atom is nitrogen). Of these two the α,β -oxiranyl esters, also called glycidic esters, are the most well known. The classic glycidic ester synthesis is the Darzen's synthesis,³⁵ and in this preparation, nucleophilic addition of the enolate of a α -halo ester, **I-26**, to a carbonyl compound (Equation 11) gives the addition product, **I-27**. Subsequent intramolecular displacement of the halide by the alkoxide oxygen provides the glycidic ester (Strategy B, Figure 4). Unfortunately, base-catalyzed self-condensation can compete with carbonyl addition. Better results are obtained using α -bromo esters and lithium bis(trimethylsilyl) amide³⁶ or sodium hydride in acetonitrile.³⁷



Equation 11

A chiral version of the glycidic ester synthesis combines the stereoselectivity provided by a Evans auxiliary with the Darzen's reaction (Strategy B, Figure 4).³⁸ In contrast to the previous Darzen's reaction, where ring closure occurs spontaneously, enolates of chiral α -haloacyl oxazolidinones, **I-28**, are reacted with aldehydes to afford β -hydroxy- α -bromo

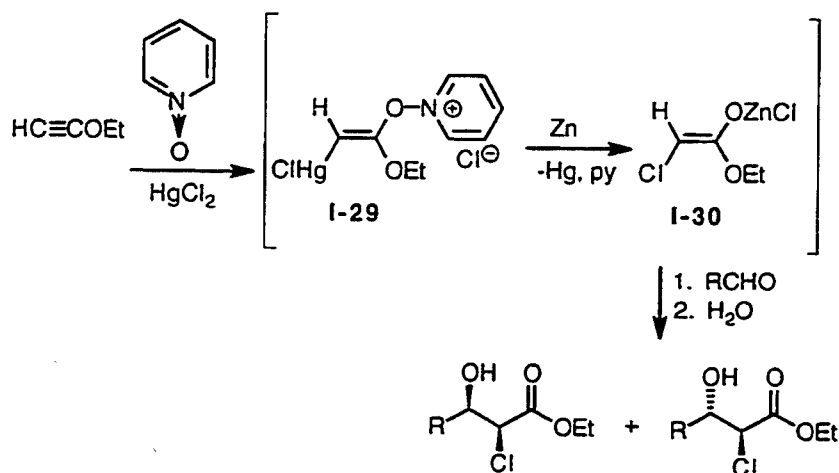
esters (Equation 12). Treatment with base causes ring closure to afford the glycidic esters, and the total yields of the reaction are dependent on the reaction conditions.



Equation 12

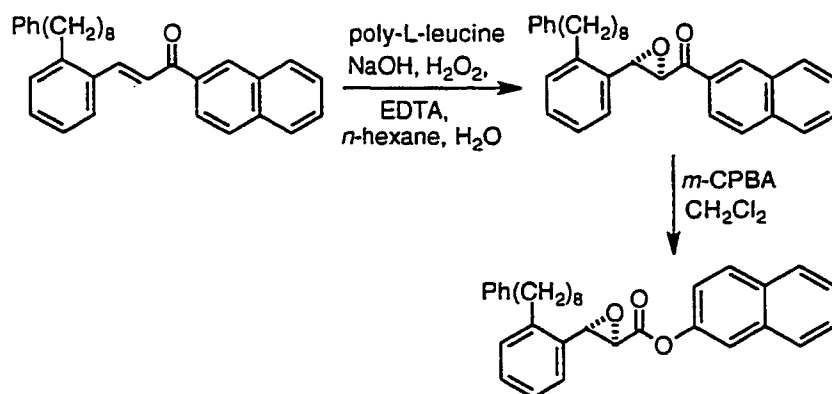
Another variation of the Darzen's glycidic ester synthesis utilizes the reaction of chlorozinc ester enolate, **I-30** with aldehydes to provide β-hydroxy-α-chloro-esters as a diastereomeric mixture (Equation 13).³⁹ The zinc enolate, **I-30**, is prepared from the reductive cleavage of the nitrogen-oxygen bond of the pyridinium salt, **I-29**, synthesized by the reaction of ethoxyacetylene with pyridine-1-oxide in the presence of mercury (II) chloride. As in the previous example (Equation 12), ring closure doesn't occur until treatment with sodium ethoxide. This type of intramolecular ring closure has been employed for other similar 1,2,3-trifunctional group arrays. Another chiral synthesis involves base induced ring closure of α-hydroxy-β-bromo-acids prepared from threonine.^{40,41,42} Other similar processes begin with the

reduction of β -keto- α -chloro esters⁴³ and β -chloro- α -keto esters⁴⁴ followed by treatment with sodium ethoxide (Strategy E, Figure 4).



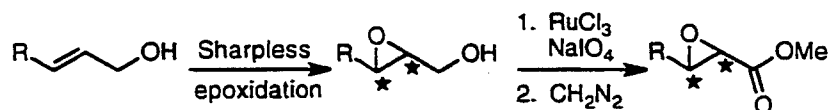
Equation 13

Epoxidations of α,β -unsaturated esters, α,β -unsaturated ketones, and allylic alcohols have also been used in the preparation of glycidic esters (Strategy C, Figure 4). Some of these methods include the diastereoselective oxidation of α,β -unsaturated esters with *m*-chloroperbenzoic acid, *m*CPBA,⁴⁵ and the highly enantioselective oxidation of α,β -unsaturated esters catalyzed by Mn(III) complexes.¹⁵ An effective synthesis of optically active aryl glycidic esters involves the Julia epoxidation of chalcones to afford oxirane ketones that undergo Baeyer-Villiger oxidation to afford glycidic esters (Equation 14).⁴⁶



Equation 14

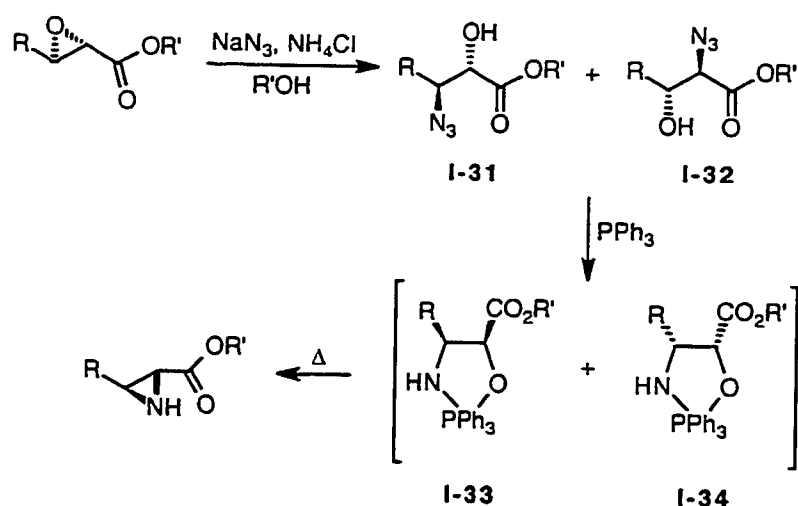
Another widely used and stereoselective glycidic ester synthesis is the stereoselective oxidation of allylic alcohols developed by Sharpless^{47,48} to afford epoxy alcohols (Equation 15).^{16,49,50,51} The resulting optically active epoxy alcohols are then oxidized to give the glycidic ester.



Equation 15

Glycidic esters are themselves useful synthetic intermediates for the preparation of β -amino- α -hydroxy esters and aziridiny esters (Structures IIIa and IIIb, Figure 3). Most commonly employed glycidic ester reactions involve ring opening reactions with amines or azides. For example, treatment of chiral glycidic esters, prepared by the Sharpless procedure (Equation 15),

with sodium azide opens the oxirane ring in an S_N2 manner to give both possible regioisomers of the azido alcohols, **I-31** and **I-32**, in chiral form (Equation 16).⁴⁹ Reduction of **I-31** and **I-32** by triphenylphosphine initially forms oxazaphospholidines, **I-33** and **I-34**, which under reduced pressure distillation afford the aziridine-2-carboxylic esters. Not many general and versatile procedures of aziridine-2-carboxylic esters are known.

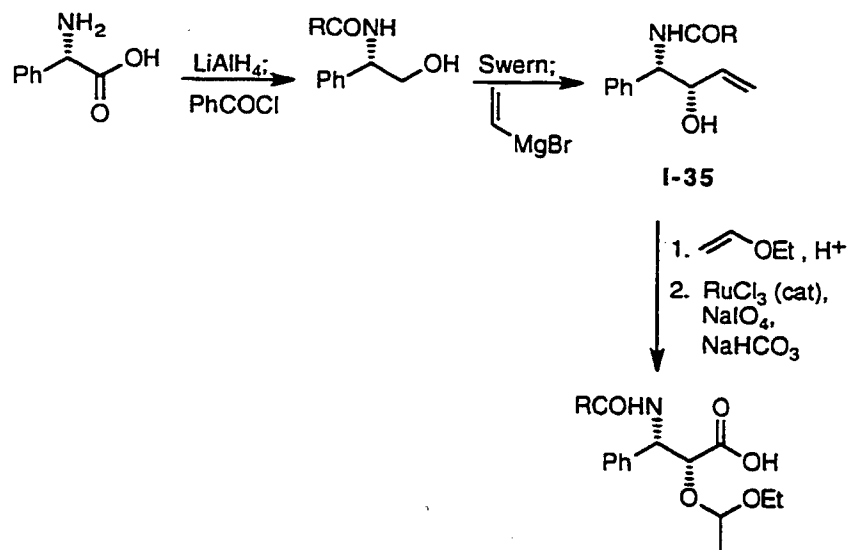


Equation 16

Besides serving as intermediates for aziridine 2-carboxylic esters, β -azido- α -hydroxy esters, **I-31** and **I-32**, are also useful intermediates for the preparation of β -amino- α -hydroxy esters (Structure IIIb, Figure 3) by hydrogenation of **I-31** and **I-32**.^{16,51,52,53} Another ring opening reaction of glycidic esters by amine nucleophiles offers entry into β -amino- α -hydroxy

esters.^{15,44,50,54} Both of these nucleophilic ring opening reactions have been used in the preparation of the C₁₃ side chain of taxol.^{15,16,51,52}

Nucleophilic amine and azide ring opening of glycidic esters is only one route to β -amino- α -hydroxyesters. A common starting material for the preparation of β -amino- α -hydroxyesters is *N*-protected- α -amino aldehydes that are readily accessible from α -amino acids. In the first step, α -amino acids are reduced by lithium aluminum hydride and protected to give a *N*-protected α -amino alcohol, **I-35** (Equation 17).⁵⁵ A tandem Swern oxidation followed by a nucleophilic addition of a vinyl Grignard reagent to the α -*N*-protected-amino aldehyde affords the allylic *threo* amino alcohol, **I-35**,

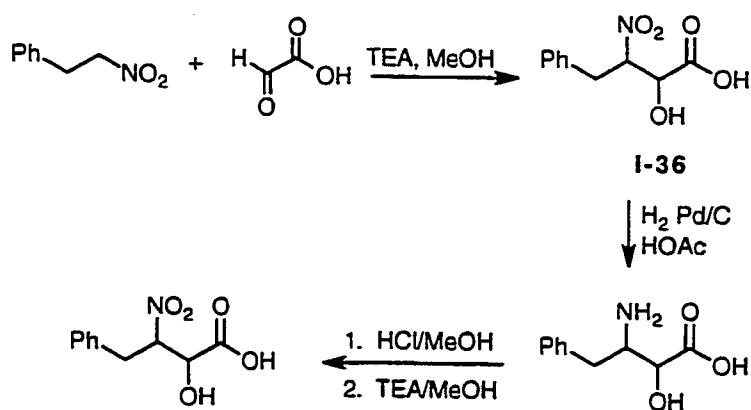


Equation 17

(Strategy A, Figure 4). The alcohol oxygen of **I-35** is protected, and the β -amino- α -hydroxy acid is obtained by oxidative cleavage using sodium

periodate and catalytic ruthenium chloride. In a similar reaction, the *N*-protected- α -amino aldehyde is treated with potassium cyanide followed by hydrolysis and esterification to provide the desired product.^{9,56,57,58} Both of these methods involve bond formation between C₁ and C₂ (Strategy A, Figure 4).

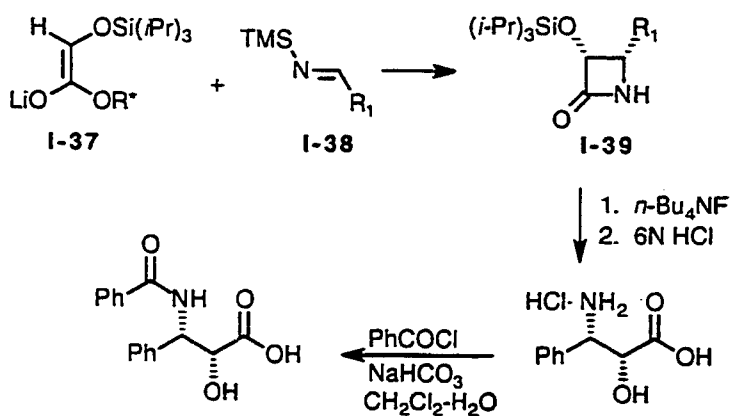
A different approach to β -amino- α -hydroxy esters involves the condensation of nitroalkanes with glyoxylic acid monohydrate (Strategy B, Figure 4) to give a β -nitro- α -hydroxy acid, **I-36**.⁵⁹ Reductive hydrogenation of the nitro group of **I-36** affords the β -amino- α -hydroxy acid, and Fischer esterification followed by neutralization with triethylamine provides the β -amino- α -hydroxy ester (Equation 18).



Equation 18

Besides the chiral Sharpless epoxidation reaction, other chiral procedures that lead to C₁₃ side chain of taxol have also been developed. Two of these methods include the Sharpless (Strategy C, Figure 4)

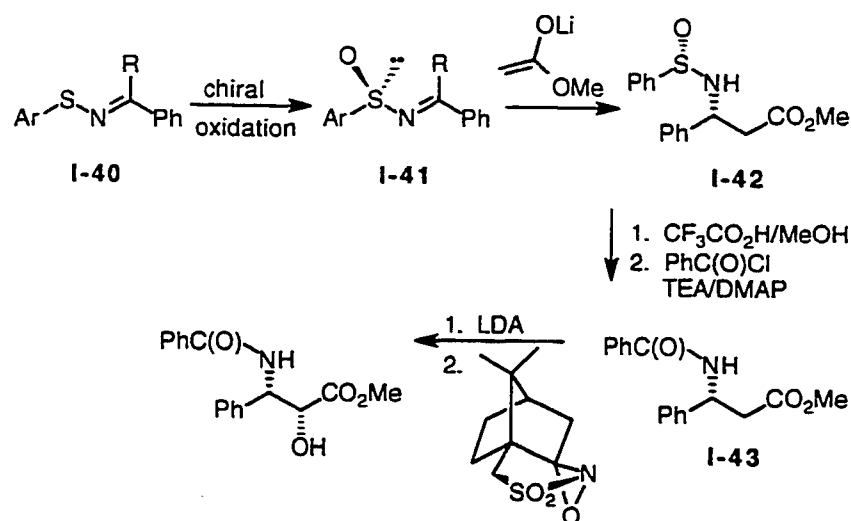
oxyamination of unsaturated esters⁶⁰ and the chiral ester enolate--imine cyclocondensation (Strategy B, Figure 4) developed for the synthesis of β -lactams⁶¹. The latter method utilizes the reaction of a chiral lithium ester enolate, **I-37**, with a *N*-(trimethylsilyl)imine, **I-38**, to afford chiral *cis*- β -lactams, **I-39** (Equation 19). Deprotection of the hydroxyl group of **I-39** followed by hydrolysis affords the β -amino- α -hydroxy acid as the hydrochloride salt. The synthesis is completed by benzoylation of the β -amino group by the Schotten-Baumann procedure to afford the enantiomerically pure *N*-benzoyl-(2*R*,3*S*)-phenylisoserine.



Equation 19

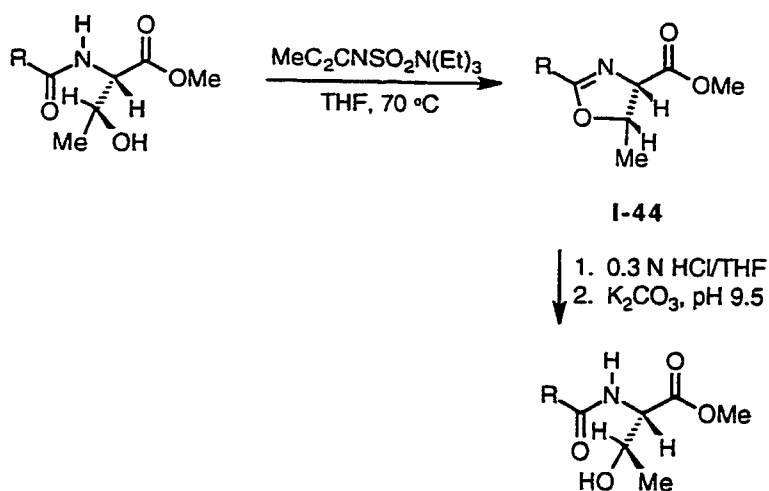
A different approach to the C₁₃ side chain of taxol utilizes sulfinimines as chiral ammonia imine synthons as precursors to β -amino- α -hydroxy acids.⁶² The reaction sequence begins with the asymmetric oxidation of sulfenimines, **I-40**, to afford the sulfinimines, **I-41** (Equation 20), and addition of ester enolates to **I-41** provides sulfinamides, **I-42**. Subsequent one-pot

hydrolysis and benzoylation of **I-42** affords chiral *N*-protected β -amino esters, **I-43**. The enolate of **I-43** undergoes hydroxylation with (+)-(camphoryl-sulfonyl)oxaziridine to provide the methyl ester of *N*-benzoyl-(2*R*,3*S*)-phenylisoserine (Strategy D, Figure 4). Another versatile asymmetric synthesis for the preparation of β -amino- α -hydroxy esters uses the Evans auxiliary with enolates of protected α -amino imides.^{63,64} This is similar to the asymmetric oxazolidinone aldol approach used for the synthesis of α,β -dihydroxy esters (Equation 4).³



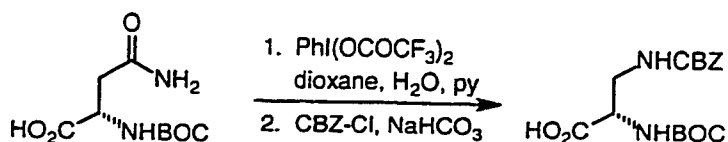
One of the simplest methods to the isomeric β -hydroxy- α -amino esters is the reduction of β -oxo- α -amino esters (Strategy E, Figure 4) (Equation 9).^{32,33} Other routes to chiral β -hydroxy- α -amino esters include the clever

conversion of threonine to *allo*-threonine and *D-allo*-threonine by fundamentally an inversion of the β -stereocenter.⁶⁵ Treatment of *N*-protected threonine with Burgess Reagent induces intramolecular cyclization that proceeds with inversion of C_3 to afford oxazoline, **I-44** (Equation 21). The acid hydrolysis of **I-44** provides an intermediate *O*-acyl amine that undergoes intramolecular *O*- \rightarrow *N*-acyl shift by adjustment of the pH to give *allo*-threonine.



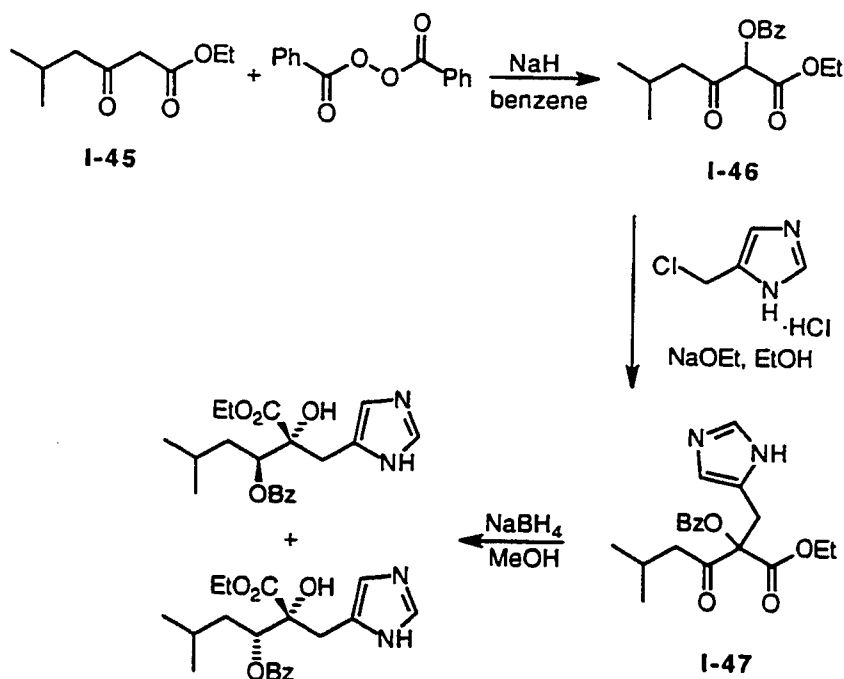
Equation 21

Not many reports for the synthesis of α,β -diamino esters have been made. One interesting procedure for the synthesis of α,β -diamino esters involves the Hoffmann degradation reaction of the (BOC) protected L-asparagine with bis(trifluoroacetoxy)-iodobenzene followed by acylation with benzylchloroformate gives the α,β -diprotected- α,β -diamino acid (Equation 22).⁹ This procedure was used in the synthetic sequence leading to cyclotheonamide **B**, **2**.



Equation 22

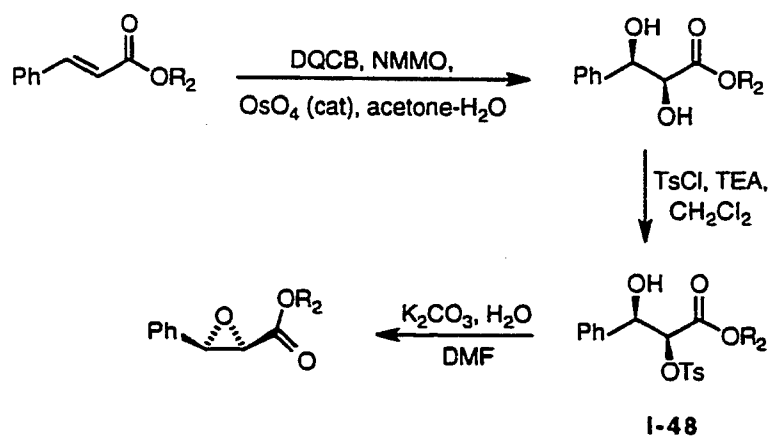
In contrast to α,β -diamino esters, α,β -dihydroxy esters have received more synthetic interest. One procedure for the synthesis of leuhistin⁵³ utilizes alkylative oxidation of β -ketoester, **I-45**, with benzoyl peroxide at the α -position (Strategy D, Figure 4) to give a β -keto- α -benzyloxy ester, **I-46** (Equation 23). An additional alkylation of **I-46** with (chloromethyl)-imidazole



Equation 23

hydrochloride finishes the construction of the carbon skeleton affording **I-47**. Reduction of **I-47** with sodium borohydride provides a diastereomeric mixture of *syn:anti* (3:1) isomers β -benzyloxy- α -hydroxy esters where the benzoate group has migrated to C₃.

The most common procedure of preparation α,β -dihydroxy esters is by the *bis*-hydroxylation of α,β -unsaturated acid derivatives. For example, treatment of cinnamic acid with osmium tetroxide provides the α,β -bis-hydroxylated acid (Strategy C, Figure 4).⁶⁶ A chiral procedure for the synthesis of α,β -dihydroxy esters (Equation 24) utilizes the Sharpless asymmetric dihydroxylation of unsaturated esters (Strategy C, Figure 4).^{52,67} The α,β -dihydroxy esters can be used as intermediates for the preparation of glycidic esters. Selective monotosylation at the α -position provides the β -hydroxy- α -tosyloxy ester, **I-48**, (Equation 24). Ring closure initiated by treatment with base yields the glycidic ester. This method was used as



Equation 24

another route to the C₁₃ side chain of taxol.⁵² As mentioned before (Equation 4), an elegant chiral procedure for the generation of α,β -dihydroxy esters utilizes the aldol reaction of a boron enolate of imide prepared from an α -hydroxy acid with an aldehyde (Strategy B, Figure 4).^{3,68}

As some of the previous examples indicate, it is often difficult to selectively manipulate one functionality without also transforming another functional group. This is especially true for structures I and III (Figure 3) that have two carbons at the same oxidation level. As a consequence, extensive protection and deprotection efforts must be employed, and the majority of the steps in the chemical sequence involve protecting group manipulation rather than functional group manipulation. Each protection and deprotection requires two additional steps in the total sequence. This wastes time and lowers the overall efficiency of the process markedly.

Recently, a new approach to polyfunctional molecules based on differential reactivity has been under investigation. The underlying premise of this approach utilizes the inherent reactivity differences in different oxidation levels. If each carbon of a 1,2,3-trifunctional array is at a different oxidation level, each carbon should undergo different types of reactions. Ideally, there would be no interference from other functional groups, and consequently, the need for differential protection and deprotection steps is minimized. The benefit of this approach is increased overall yield, increased atom efficiency, and decreased preparation time. Of the structures previously considered, both structure IIa and structure IIb (Figure 5) meet the criteria of this approach. As can be seen from the review of the literature, there are only a few examples for the synthesis of this array of functionalities.

As drawn, structures IIa and IIb (Figure 5) would not serve well as intermediates to other 1,2,3-trifunctionalized compounds because of the hetero atoms contained in the functional groups Y and Z. As described earlier, nitrogen or oxygen in the alcohol oxidation state are potential nucleophiles. Installation of these hetero atoms late in the sequence is generally prudent, thus synthetic intermediates leading to these structures are required which would have either Y or Z as a good leaving group. With the proper choice of leaving group, selective attachment of the desired hetero atom could be achieved, and the intermediate would be synthetically versatile.

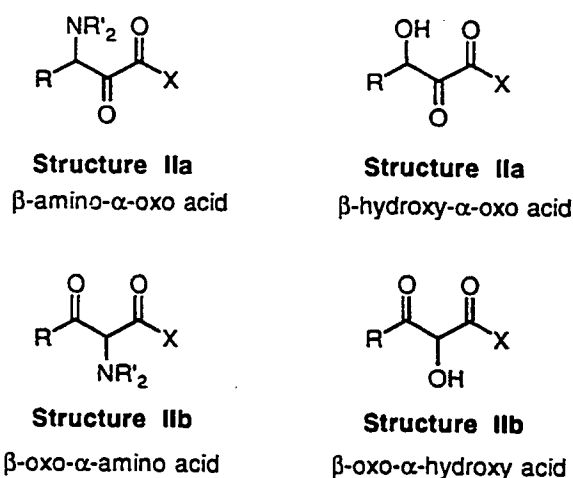
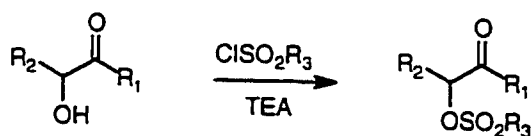


Figure 5. Possible Differential Reactivity Structures

Two common choices for leaving groups are halides and sulfonyloxy groups, and there are several examples of 1,2,3-trifunctionalized compounds containing halide leaving groups.^{29,38-44,69} In contrast, sulfonyloxy groups are

also excellent leaving groups, but placing sulfonyloxy leaving groups in the 1,2,3-trifunctional environment has little precedent.^{52,67} The chemistry of halide or sulfonyloxy substituted 1,2,3-trifunctionalized intermediates can be extrapolated from the known chemistry of halogen or sulfonyloxy substituted 1,2-difunctional molecules. Some of the more interesting preparations and reactions of α -halo carbonyl compounds and α -sulfonyloxy carbonyl compounds will be considered.

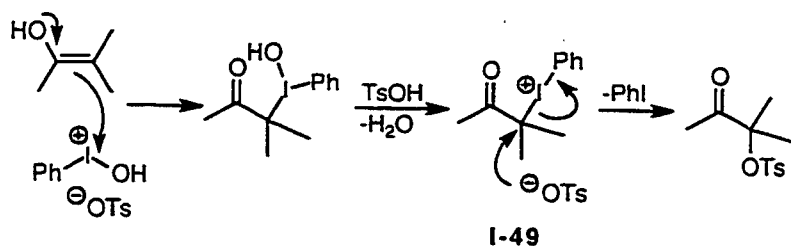
α -Halo carbonyl compounds are useful synthetic intermediates, and many studies of the preparation of these substances have been carried out.⁷⁰ In general, α -halo carbonyl compounds can be easily accessed by the reaction of enol derivatives with halogens.^{71,72} On the other hand, preparation of α -sulfonyloxy carbonyls can be achieved by two methods. One method for the preparation of α -sulfonyloxy carbonyl compounds involves the condensation of 2-hydroxy carbonyl compounds with sulfonyl chlorides (Equation 25).^{73,74} This procedure is limited by the availability of the α -hydroxy carbonyl compounds, and while α -sulfonyloxy esters can readily be prepared by this route, the reaction of α -hydroxy ketones with sulfonyl chlorides is problematic due to base-promoted decomposition.



Equation 25

A second approach to α -sulfonyloxy carbonyl compounds involves oxidative attachment of the sulfonyloxy group to the α -position of the carbonyl

derivative by use of an electrophilic equivalent of the sulfonyloxy group. Reagents that have been utilized for this purpose are hypervalent iodine reagents and sulfonyl peroxides. Hypervalent iodine reagents⁷⁵ have been used to oxidatively attach tosyloxy, mesyloxy, and triflyloxy groups to the α -position of carbonyls by reaction with the enol derivatives of carbonyl compounds (Equation 26). This procedure is advantageous for reactions of carbonyl compounds with low enol contents. The attacking electrophile is an electron deficient iodine species, [hydroxy(tosyloxy)iodo]-benzene, and an iodonium intermediate, **I-49** is produced. The tosyloxy group attacks **I-49** to give the α -sulfonyloxy carbonyl with loss of iodobenzene.

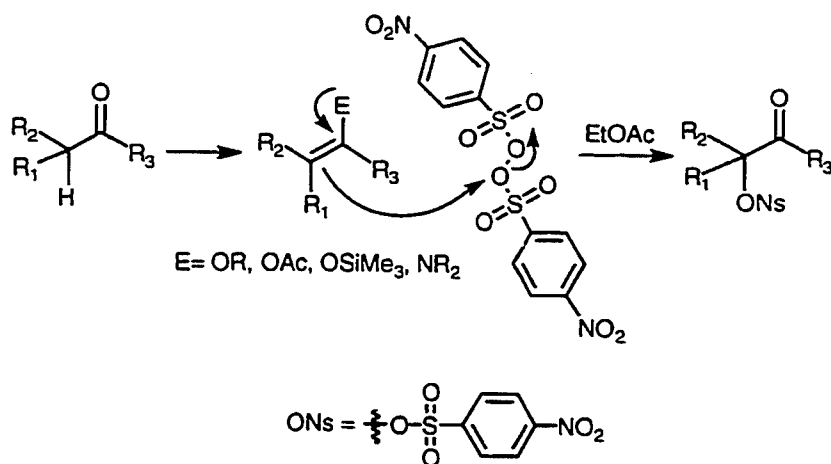


Equation 26

Sulfonyl peroxides have also been used for the preparation of α -sulfonyloxy carbonyls by electrophilic oxidative attachment of (arylsulfonyl)oxy groups to electron rich enol derivatives.⁷⁶ One particularly useful sulfonyl peroxide, is *bis*((*p*-nitrophenyl)sulfonyl) peroxide, *p*-NBSP, which has been successfully used in reactions (Equation 27) with enol derivatives such as enol ethers,⁷⁷ enol acetates,⁷⁸ silyl enol ether and enamines⁷⁹ ketene silyl acetals,⁸⁰ silyl enol ethers of α,β -unsaturated esters.⁸¹ In contrast to the

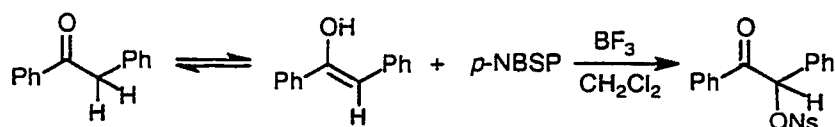
hypervalent iodine reagents, the enol derivatives of the carbonyl must be pre-formed before reaction with the sulfonyl peroxide.

All of these reactions require the synthesis of the stable enol derivatives from the carbonyl compound. A more efficient route to α -nosyloxy carbonyls would be the direct reaction of the enol form with *p*-NBSP. The



Equation 27

success of this approach depends on an inherently high enol content of the carbonyl compound. The enol content of the carbonyl must be sufficiently high in order to sustain the bimolecular addition reaction with *p*-NBSP because the competing reaction is the decomposition of the *p*-NBSP. This was demonstrated by the reaction of deoxybenzoin with *p*-NBSP in the presence of boron trifluoride etherate (Equation 28).⁷⁹ Simple ketones, such as cyclohexanone and acetophenone, did not afford α -nosyloxy ketones directly because of their low enol contents.

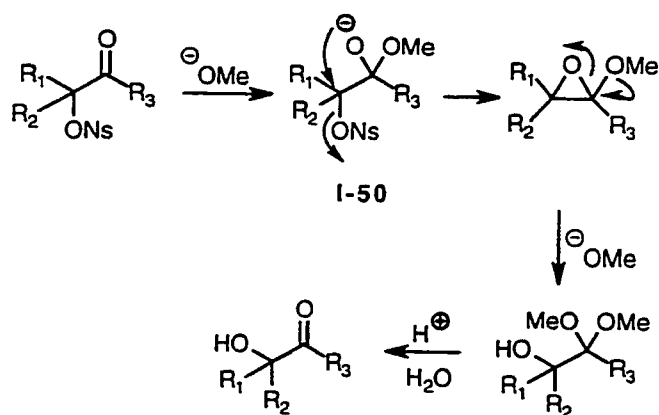


Equation 28

The reactivity of α -halo carbonyl compounds is different than typical alkyl halides. An electron withdrawing group such as a carbonyl group α to the halide group⁸² enhances substitution and elimination pathways generally through an inductive effect. Moreover, attachment of a halide next to a carbonyl group increases the electrophilicity of the carbonyl group. Consequently, the reactions of α -halo ketones with bases and nucleophiles are often complex, and there are six different reaction pathways possible. The pathway followed depends upon the halogen present, the presence of protons α and β to the carbonyl group and the reaction conditions used.

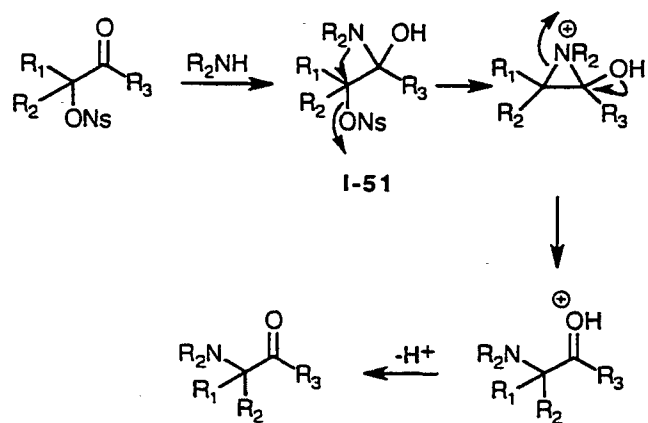
Compared to the six different pathways known for the reaction of α -halo ketones with nucleophiles and bases,⁸² the reaction of α -sulfonyloxy ketones is greatly simplified.⁷⁶ α -Nosyloxy ketones tend to undergo two basic transformations. The first transformation is due to the enhanced electrophilicity of the carbonyl group. Nucleophiles add to the carbonyl group, and the resulting tetrahedral intermediate decays by nucleophilic displacement of the nosylate. For example, reaction of α -nosyloxy ketones with methanol and potassium carbonate (Equation 29), provides α -hydroxy ketones.⁸³ Nucleophilic addition of methoxide to the carbonyl group gives a tetrahedral intermediate, I-50. Subsequent intramolecular displacement of

nosylate followed by acidic, hydrolytic work-up provides an α -hydroxy ketone. In contrast, this process is a minor pathway of α -halo ketones.



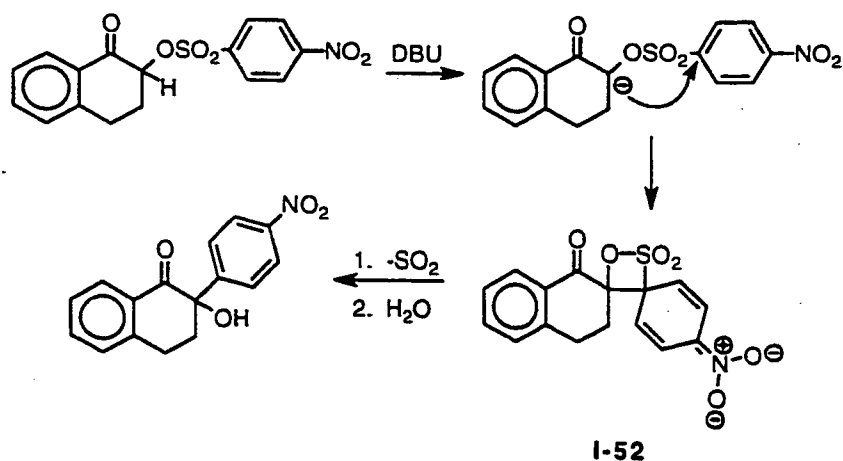
Equation 29

The reaction of α -nosyloxy ketones with other nucleophiles has also been studied. Amines also undergo nucleophilic addition to the carbonyl of α -nosyloxy ketones to afford the tetrahedral intermediate, **I-51** (Equation 30).⁸³ In such cases, the nosylate is displaced by the amine, and α -amino ketones are obtained. Recently, sodium azide⁸⁴ was found to displace the nosylate group of α -nosyloxy ketones in high yields, but the reaction is believed to occur by azide ion attack directly on the α -carbon and not by attack on the carbonyl.



Equation 30

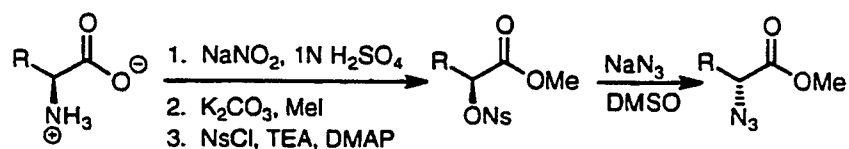
A second reaction pathway of α -nosyloxy ketones is observed upon treatment with non-nucleophilic bases. The products are α -*p*-(nitrophenyl)- α -hydroxy carbonyls (Equation 31).⁸³ The combination of the electron



Equation 31

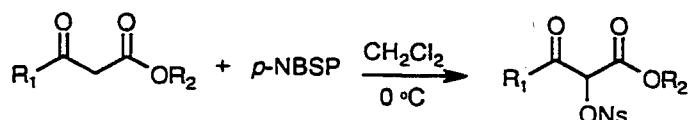
withdrawing ability of both the carbonyl group and the α -nosyloxy group, greatly acidify the α -proton. For example, enolate formation of α -nosyloxy tetralone followed by intramolecular addition to the *p*-nitrobenzenesulfonyloxy group in an *ipso* fashion forms a four-membered ring, Meisenheimer intermediate, **1-52**. The intermediate **1-52** collapses with loss of sulfur dioxide to provide the α -*p*-(nitrophenyl)- α -hydroxy tetralone.

Chiral α -nosyloxy esters, prepared from chiral α -hydroxy esters, were found to give chiral 2-hydrazinyl esters upon reaction with *t*-butyl carbazate.⁸⁵ Alkyl α -nosyloxy β,γ unsaturated esters were also found to react with amines by direct displacement of the nosylate group.⁸¹ In an elegant chiral synthesis, D- α -amino acids were prepared from L- α -amino acids by inverting the configuration of the α -carbon (Equation 32).⁸⁶ The key intermediate, a chiral α -nosyloxy ester, was treated with sodium azide to afford the (*R*)-2-azido esters. Staudinger reaction with the (*R*)-2-azido esters afforded the D- α -amino acids. In contrast to α -nosyloxy ketones, the substitution mechanism for α -nosyloxy esters with nucleophiles probably occurs by simple substitution.^{85,86} In summary, α -nosyloxy carbonyls react with nucleophiles to give α -substituted carbonyls and with non-nucleophilic bases to afford α -*p*-(nitrophenyl)- α -hydroxy carbonyls.



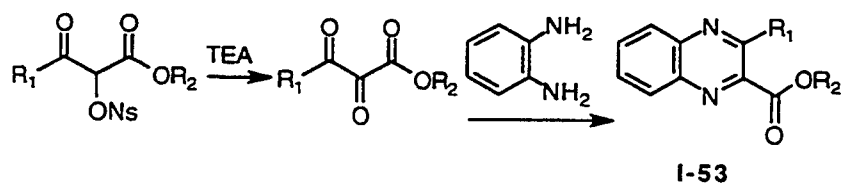
Equation 32

Recently, 1,2,3-trifunctionalized intermediates, β -keto- α -nosyloxy esters (structure IIb, Figure 5), have been effectively prepared (Equation 33) from the reaction of β -keto-esters and *p*NBSP (Strategy D, Figure 4).^{87,88,89} As was the case with deoxybenzoin (Equation 28), the enol content of the β -keto esters was sufficient to support the bimolecular addition reaction in methylene chloride at 0 °C; however, β -diesters with lower enol content did not react well with the *p*-NBSP.⁷⁶ β -Keto α -nosyloxy amides (structure IIb, Figure 5),⁹⁰ were also prepared by the reaction of the β -keto amide and *p*-NBSP with zinc chloride in ethyl acetate at -78 °C. The ease of preparation of β -keto- α -nosyloxy esters led to the investigation of their reactions.



Equation 33

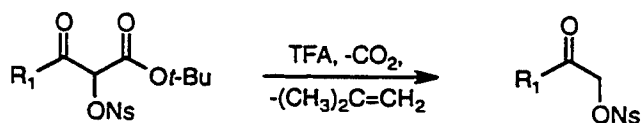
β -Keto- α -nosyloxy esters and β -keto- α -nosyloxy amides were found to undergo a variety of transformations to give other 1,2,3-trisubstituted products. Reaction of β -keto- α -nosyloxy esters⁹¹ with triethylamine gave 1,2,3-tricarbonyl esters (Equation 34), by base promoted, reductive elimination (Strategy E, Figure 4). The 1,2,3-tricarbonyl compound was not isolated, but the 1,2,3-tricarbonyl could be trapped in situ by treatment with *o*-phenylenediamine. Likewise, treatment of β -keto- α -nosyloxy amides⁹⁰ with DBU provided 1,2,3-tricarbonyl amides that were also trapped with *o*-phenylenediamine to give **1-53**. In contrast to the β -keto- α -nosyloxy esters, the



Equation 34

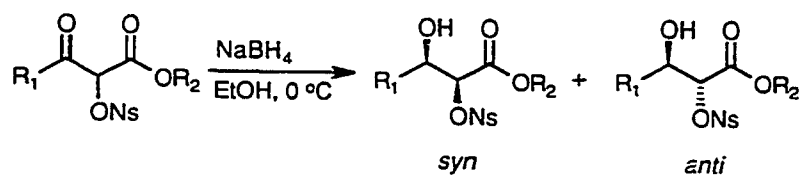
reaction of β -keto- α -nosyloxy amides with triethylamine and diisopropylamine did not provide the 1,2,3-tricarbonyl compound.⁹⁰

t-Butyl β -keto- α -nosyloxy esters derivatives are a special class of β -keto- α -nosyloxy esters and were found to decarboxylate when treated with trifluoroacetic acid to afford α -nosyloxy ketones (Equation 35).^{87,89} The *t*-butoxycarbonyl group directs the electrophilic oxidative attachment of the nosyloxy group and is removed in the final step. In contrast to the other methods for the preparation of α -nosyloxy ketones (Equation 26 and Equation 27), this method allows for the regiospecific preparation of α -nosyloxy ketones, and the regiospecific enol derivative does not have to be prepared.



Equation 35

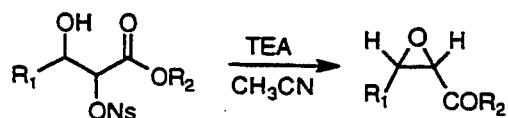
Reduction of β -keto- α -nosyloxy esters by sodium borohydride provides β -hydroxy- α -nosyloxy esters in good yields as a mixture of *syn* and *anti* diastereomers (Equation 36).⁹¹ The diastereomers are separable by HPLC



Equation 36

and are distinguishable by ^1H NMR spectroscopy, but assignment of the *syn* and *anti* stereochemistry could not be done based upon chemical shifts and coupling constants.

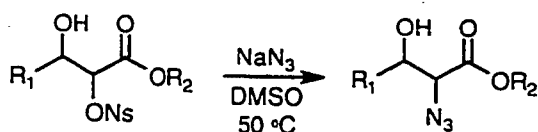
β -Hydroxy- α -nosyloxy esters are versatile intermediates. Reaction of the β -hydroxy- α -nosyloxy esters with triethylamine in acetonitrile provides a mixture of the *cis* and *trans* glycidic esters (Equation 37).⁹¹ The ring closure is stereoselective. The *syn* reduction product provides the *cis*-glycidic ester and the *anti* reduction product affords the *trans*-glycidic ester. The coupling constants and chemical shifts of the glycidic esters allow assignment of the *cis* and *trans* isomers, and therefore, the major diastereomer produced in the reduction with sodium borohydride is assigned as the *syn* isomer.



Equation 37

Since the reaction of β -hydroxy- α -nosyloxy esters with triethylamine provides ring closure, most amine nucleophiles would be unsuitable as nucleophiles. As is the case for α -nosyloxy esters (Equation 32), reaction of

β -hydroxy- α -nosyloxy esters with a weakly basic amine equivalent, sodium azide, affords the β -hydroxy- α -azido esters in fair yields (Equation 38). The reaction is stereoselective, but about 25% epimerization is found to have occur at the α -carbon. In summary, β -keto- α -nosyloxy esters are found to be versatile intermediates for the preparation of 1,2,3-tricarbonyls and β -hydroxy- α -nosyloxy esters, and β -hydroxy- α -nosyloxy esters are themselves intermediates for the preparation of glycidic esters.

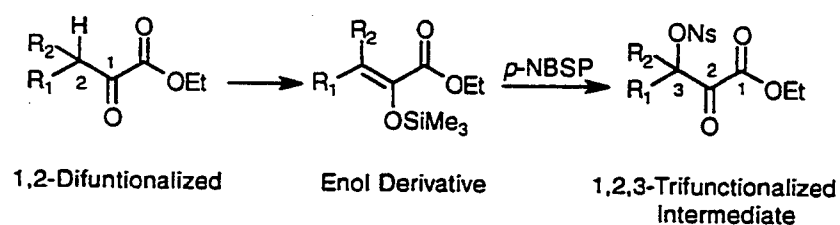


Equation 38

While 1,2,3-trifunctionalized intermediates with structure IIb (Figure 5) have been prepared and found to be very versatile and useful synthetic intermediates, 1,2,3-trifunctionalized intermediates with structure IIa (Figure 5) have not been prepared or investigated to any extent. This is probably due to the fact β -ketoesters are well known compounds that have been extensively studied while only recently have α -ketoesters become more widely available. Based on the synthetic versatility of β -oxo- α -nosyloxy esters, it was envisioned that β -nosyloxy- α -keto esters could also prove to be interesting and effective synthetic intermediates for the preparation of 1,2,3-trifunctionalized compounds.

3. RESEARCH OBJECTIVES

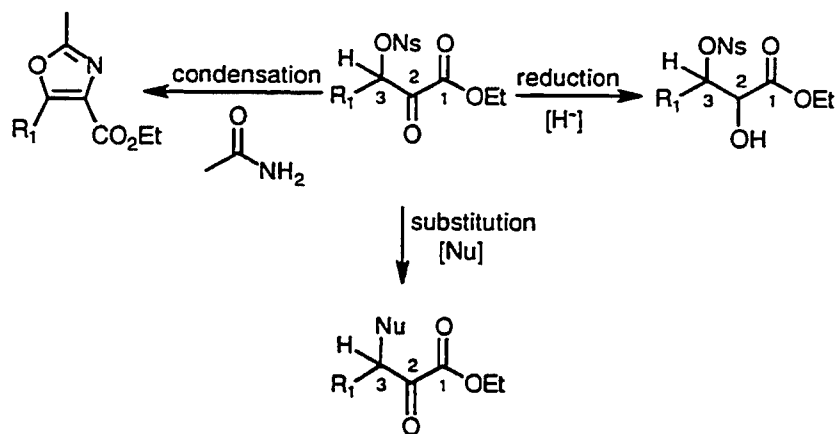
This research has two main objectives. The first is to develop a synthesis of β -nosyloxy- α -ketoesters from α -keto esters based upon oxidative attachment of the nosyloxy group to the β -position of the α -keto ester utilizing the electrophilic reagent, *p*-NBSP, (Equation 39). This method requires the α -keto ester to function as a nucleophile, and since α -keto esters are not inherently nucleophilic, the reactivity of the α -keto esters must be altered by conversion into nucleophilic enol derivatives. Synthetic methods for the preparation of these electron rich enol derivatives had received little attention, thus far.



Equation 39

The second main objective of this research is to examine the utility of β -nosyloxy- α -keto esters as synthetic intermediates for the synthesis of other interesting 1,2,3-trifunctionalized compounds. The chemistry of β -nosyloxy- α -keto esters should be dictated by two structural features of these compounds, the electrophilic carbonyl group and the excellent leaving group ability of the nosylate. Traditional transformations of the carbonyl group such as nucleophilic addition and reduction will be examined. Reduction of the

carbonyl group would afford β -nosyloxy- α -hydroxyesters, which when treated with base, could potentially undergo ring closure to afford glycidic esters. The ability of the nosylate to act as a leaving group will be examined by reaction with nucleophiles. The juxtaposition of these two reactive groups next to each other provides the opportunity for unusual chemistry, and methods for a combination of both of these chemistries by condensation reactions will be examined (Equation 40).



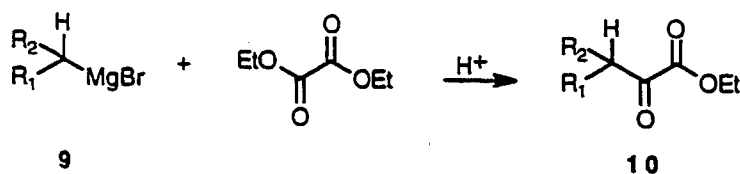
Equation 40

4. RESULTS

4.1 Preparation of 3-[[(*p*-Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters

A variety of α -keto esters (Table I) were chosen to examine the effects of structural changes on the conversions of these compounds into 1,2,3-trifunctionalized derivatives and subsequent conversions into other, biologically interesting 1,2,3-trifunctionalized molecules. While methyl pyruvate, **10a**, has been commercially available for some time, only since the inception of this project have other α -keto esters become commercially available. Those α -keto esters besides **10a** that are commercially available are ethyl 4-phenyl-2-oxobutyrate, **10b**, diethyl oxalpropionate, **10d**, and ethyl 3-methyl-2-oxobutyrate, **10e**. Since only a limited number of α -keto esters can be purchased, other α -keto esters including ethyl 2-oxo-octanoate, **10c**, ethyl cyclohexylglyoxylate, **10f**, and ethyl 3-phenyl-pyruvate, **10g**, were synthesized.

One of the most versatile methods for the synthesis of α -keto esters is the reaction of an alkyl Grignard reagent, **9**, with diethyl oxalate (Equation 41).⁹² Yields for this reaction typically range from 50-75%, and possible



Equation 41

structures are limited only by the availability of the Grignard reagent. Recently, even vinyl Grignard reagents have been reported to give good yields.⁹³

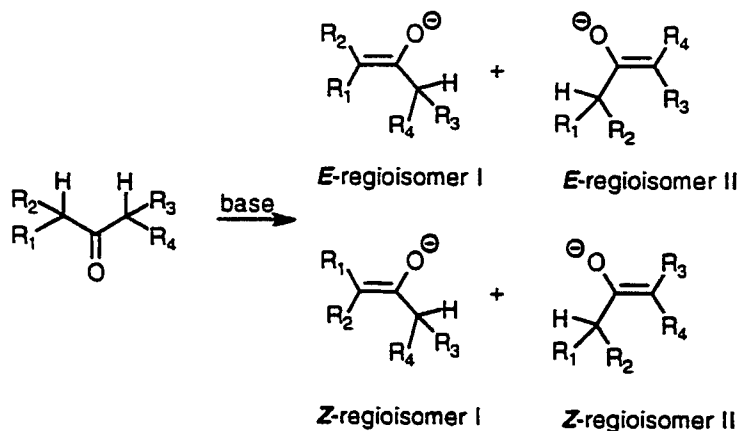
Table 1. Availability of α -Keto Esters

Structure	R ₁	R ₂	R ₃	Commercial Availability
10a	H	H	Me	yes
10b	CH ₂ Ph	H	Et	yes
10c	<i>n</i> -pentyl	H	Et	no ⁹³
10d	CH ₃	EtOCO	Et	yes
10e	CH ₃	CH ₃	Et	yes
10f	-cyclohexyl-		Et	no ⁹⁴
10g	Ph	H	Et	no ^{95,96}

There are some drawbacks with this synthesis. Prepared or purchased, the Grignard reagent, **9**, has a propensity to couple with itself to afford the dimeric hydrocarbon. Luckily, this by-product generally presents no difficulty in the purification of the α -keto ester, as it is much less polar than either the reaction product or diethyl oxalate. The major difficulty with this synthesis lies in the separation of the α -keto ester from diethyl oxalate. Frequently, the boiling points of the product and diethyl oxalate are too close to provide adequate separation using distillation, and separation by chromatography was inconvenient due to the large amounts of product that were prepared at one time. The original report of this synthesis used two

equivalents of diethyl oxalate for each mole of Grignard reagent, 9. A modification that gives higher yields of α -keto esters uses 10% excess diethyl oxalate.⁹⁷ In spite of these drawbacks, the Grignard route to α -keto esters was used to prepare the requisite α -keto esters in fair yields. This is a far better procedure than another recently reported route to α -keto esters which involves a two carbon homologation of aldehydes.⁹⁸ In our hands, this procedure yielded no product.

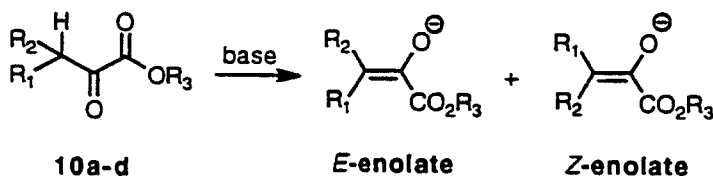
Inherently, α -keto esters are not nucleophilic enough to react with electrophiles, so the nucleophilic reactivity of the α -keto esters has to be increased by conversion into an enol derivative which can serve as an electron rich nucleophile. The preparation of silyl enol ethers from ketones normally involves the treatment of a ketone with a base of sufficient strength to afford an enolate and subsequent trapping of the enolate with a trialkylsilyl halide.⁹⁹ For asymmetrical ketones, two regioisomeric enolates (Equation 42)



Equation 42

can be formed with the possibility that each of the regioisomers has two stereoisomers, (*Z*, *E*). Arranging the R groups by the Cahn-Ingold-Prelog sequence, the highest priority is given to R₁, and the priority sequence for the R groups becomes R₁>R₂>R₃>R₄.

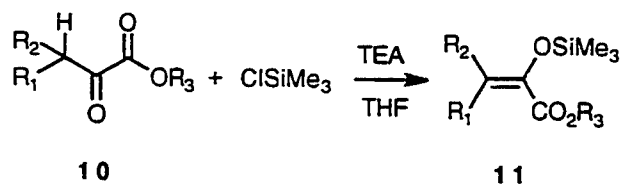
For α -keto esters, only one regioisomer is possible since the other substituent on the ketone is an ester group (Equation 43). If the R₁ and R₂ are not the same group, then the possibility of two stereoisomers, *E* and *Z* enolates, exists. Again, the same Cahn-Ingold-Prelog sequence, R₁>R₂, is used for designating the *E* and *Z* structures. For the α -keto esters used in this study, only **10b**, where R₁ = Bn and R₂ = H, and **10c**, where R₁ = *n*-C₅H₁₁ and R₂ = H, could give mixtures of the *E* and *Z* enolates. The *E* enolate from **10b** and **10c** is the structure wherein the oxygen is on the opposite side of the alkene as the alkyl chain, and the *Z* enolate has the alkyl side chain positioned on the same side of the alkene as the oxygen. The relative amounts of the stereoisomers is dictated by the relative rates of the two competing proton removal steps.



Equation 43

Two different reaction conditions were used to convert the α -keto esters to enolates. The first set of conditions employed the slow addition of triethylamine in tetrahydrofuran to a solution of the α -keto ester and

trimethylsilyl chloride in tetrahydrofuran (Equation 44).¹⁰⁰ The procedure was first reported by Creary for the synthesis of 1-carbomethoxy-1-(trimethylsiloxy)ethylene, **11a**, and the yield was slightly improved by substituting tetrahydrofuran for ether as the reaction solvent. Fair to excellent yields for silyl enol ethers **11a-d** were obtained (Table 2), and compounds 1-carboethoxy-1-(trimethylsiloxy)-3-phenylpropene, **11b**, 1-carboethoxy-1-(trimethylsiloxy)heptene, **11c**, and 1-carboethoxy-1-(trimethylsiloxy)-2-methyl-2-carboethoxyethylene, **11d**, are new compounds.



Equation 44

Some silyl enol ethers prepared from ketones have been found to be susceptible to hydrolysis, but **11a-d** are stable to hydrolytic work-up as well as silica gel chromatography. The main impurity in this procedure was found to be the starting α -keto esters, **10**, and only **11d** showed substantial amounts of the starting material (25%). As long as the triethylamine was completely removed during the work-up, the silyl enol ethers could be used as crude products without further purification. It should be noted that the yield calculated for **11d** is corrected for the concentration of **10d**. In all cases, the trimethylsilyl chloride and the triethylamine needed to be freshly distilled or poor results were obtained.

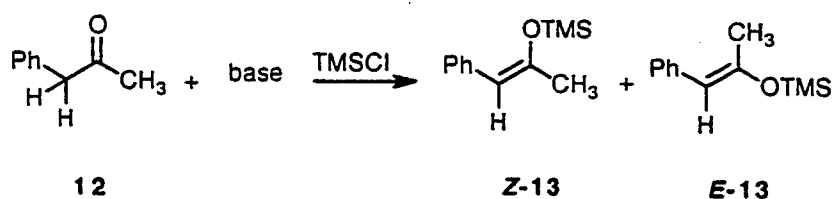
Table 2. Preparation of Silyl Enol Ethers Using Triethylamine

Product	R ₁	R ₂	R ₃	Yield (%)
11a	H	H	Me	67
11b	CH ₂ Ph	H	Et	89
11c	<i>n</i> -pentyl	H	Et	49
11d	CH ₃	EtOCO	Et	74
11e	CH ₃	CH ₃	Et	5
11f	-cyclohexyl-		Et	7

Unfortunately, **10e** and **10f** gave little conversion to the corresponding silyl enol ether when treated with triethylamine and trimethylsilyl chloride (5% and 7% respectively). It was initially thought that **11e** and **11f** were more sensitive to hydrolysis than the other products, so the reaction mixture of **11e** was not subjected to a hydrolytic work-up. This modification also produced **11e** in 5% yield, and even the use of a more stable silyl group, dimethyl-*t*-butylsilyloxy, provided no improvement. It is assumed that the same modifications to the procedure would have provided the same results for the preparation of **11f** even though these modifications were not actually tried with **10f**. Therefore, a different method for these two α -keto esters was sought.

Proper selection of reaction conditions can make a significant difference in the success of a reaction. There is a good deal of literature on the synthesis of silyl enol ethers from unfunctionalized ketones, and much of

the early work on silyl enol ether preparation from ketones was done by House.¹⁰¹ Different bases and reaction conditions were examined, and a great variability in product composition was observed under differing reactions conditions. For example, 1-phenyl-2-propanone, **12**, was treated with three different bases and trimethylsilyl chloride (Equation 45). The results from these experiments are shown (Table 3). When reacted with triethylamine, the silyl enol ether product was obtained in 42% yield with a *Z:E* ratio of 67%:33%. Use of lithium diisopropylamide gave 34% product in a *Z:E* ratio of 14%:86%, and sodium hydride gave 61% product in a *Z:E* ratio of 96%:4%. From this data, sodium hydride was clearly gave the highest conversion to a silyl enol ether, if *Z* the isomer was desired.



Equation 45

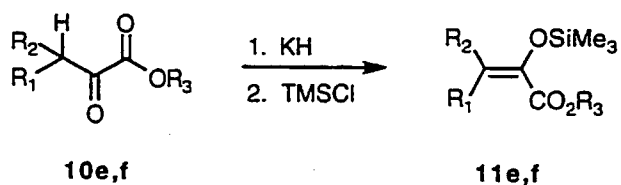
Table 3 Preparation of Silyl Enol Ethers of 1-Phenyl-2-Propanone

Base	Yield (%)	<i>Z</i> isomer (%)	<i>E</i> isomer (%)
TEA	42%	67%	33%
LDA	34%	14%	86%
NaH	61%	96%	4%

On the other hand, Stork had found sodium hydride to react sluggishly with ketones,¹⁰² and consequently, the self-condensation reaction can compete with silyl enol ether formation. A base with a little more reactivity would be a better choice, but even lithium diisopropylamide, generally regarded as the best reagent to convert ketones to enolates, afforded aldol by-products from methyl ketones.¹⁰¹ In these cases, the rate of the aldol reaction is competitive with the rate of proton removal.

Another strong base commonly used for enolate formation is potassium hydride.^{103,104,105} It was hoped that potassium hydride would have enhanced reactivity so as to convert **10e** and **10f** to their respective enolates. The reaction with **10e** and **10f** with potassium hydride (Equation 46) quickly formed enolates that were subsequently trapped with trimethylsilyl chloride in good yields (Table 4). The main impurity found for the reaction was the respective α -keto ester starting material. For the preparation of **11e**, the product mixture was found to contain 10% of **10e**, and as before, the calculated yield was adjusted for the impurity. As was suspected, **11e** and **11f** were sensitive to hydrolysis; thus, neither aqueous work-up or silica gel chromatography could be used for purification. However, the crude products were of sufficient purity to use in subsequent reactions with *p*NBSP and some purification of **11e** and **11f** with bulb to bulb distillation could be achieved if necessary.

Although it was gratifying to be able to produce all of the trimethyl silyl enol ethers, it was desirable to find one, general preparation for all of the silyl enol ethers. Since triethylamine and trimethylsilyl chloride conditions did not

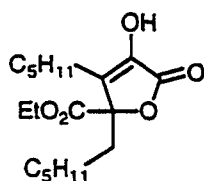


Equation 46

Table 4. Preparation of Silyl Enol Ethers Using Potassium Hydride

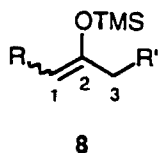
Product	R ₁	R ₂	R ₃	Yield (%)
11c	<i>n</i> -pentyl	H	Et	0
11e	CH ₃	CH ₃	Et	71
11f	-cyclohexyl-		Et	72

produce silyl enol ethers for all reactants, potassium hydride and trimethylsilyl chloride reaction conditions were examined further. Unfortunately, treatment of **10c** with potassium hydride gave self-condensation followed by ring closure to produce the unsaturated lactone, **14**, in 80% yield. Attempts to find a single procedure for the effective preparation of silyl enol ethers derivatives of α -keto esters were abandoned.



14

As described before (Equation 43), when the R_2 group of the α -keto ester is a hydrogen, as for **10b** and **10c**, the possibility of two stereoisomeric enolates, *Z* and *E*, exists. Under the reactions conditions examined, only one stereoisomer of **10b** and **10c** was produced. Various attempts to determine the stereochemistry of **11b** and **11c** were undertaken. If both the *E* and *Z* silyl enol ethers had been produced, proper assignment would have been much easier, since the geometry of other silyl enol ether derivatives have been determined by ^{13}C NMR.¹⁰⁶ For example, the ^{13}C signal of the allylic C_3 of an *E* trimethylsilyl enol ether, **8**, has been reported to have a chemical shift 5-6 ppm upfield from the *Z* isomer. However, the allylic C_3 for **11b** and **11c** is a carboethoxy group, and it is unknown if the carboethoxy group would exhibit the same type of structure and spectral relationship.



Another method used to assign the geometry of trimethylsilyl enol ethers is the NMR measurement¹⁰⁷ of the nuclear Overhauser effect, (NOE).¹⁰⁸ This technique is one of the best methods to infer internuclear distances in molecules and consequently stereochemistry of molecules in an indirect manner. The NOE effect depends upon the dipolar coupling between nuclei instead of scalar coupling (*J*-coupling). The procedure involves the measurement of change in intensity of one resonance when the transitions of another are saturated with a presaturation pulse before the acquisition of the

data. Measurement of the normal intensity of the resonance is made, I_0 , and the intensity while saturation of some other resonance is given by I . The value of the NOE, η_i , is the difference of the measurement after saturation and before the saturation, divided by the initial normal intensity ($\eta_i = (I - I_0)/I_0$). The value for η_i is multiplied by 100% to give NOE as a percent enhancement. Although this is not always the case, the measured enhancement has been found to be inversely proportional $1/r^6$, where r^6 is the distance between the two nuclei of interest. Therefore, proximate nuclei will give rise to larger NOE enhancements, and distant nuclei will not give enhancements.

It was anticipated that depending upon whether the product was the *E* or the *Z* isomer, selective pre-irradiation of the trimethylsilyl resonance would cause a NOE enhancement in the group that was on the same side of the alkene. So, if **11b** was the *E* isomer, then irradiation of the trimethylsilyl resonance would cause a corresponding enhancement of the vinyl signal (Figure 6); conversely, irradiation of the vinyl signal would cause enhancement of the trimethylsilyl signal. On the other hand, if **11b** was the *Z* isomer, selective irradiation of the trimethylsilyl resonance of *Z* isomer would give rise to an enhancement in the benzylic signal, and irradiation of the benzylic resonance would cause a corresponding enhancement in the trimethylsilyl resonance. What should be noticed is that the internuclear distance between the trimethylsilyl and the vinyl proton in **E-11b** is closer than the internuclear distance between the trimethylsilyl and the benzylic group of **Z-11b**. While selective irradiation of the trimethyl silyl and vinyl signals of **E-11b** would most likely give rise to a NOE enhancement, irradiation of the

trimethylsilyl or benzyl group of **Z-11b** may or may not cause a NOE enhancement because the internuclear distance is greater in **Z-11b** than in the **E-11b** isomer.

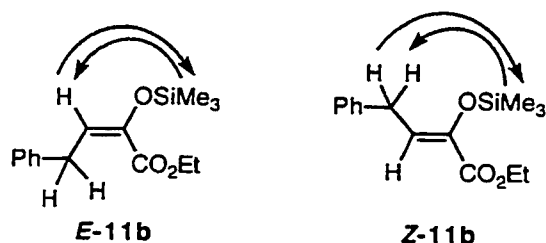


Figure 6. Possible NOE Enhancements for **E-11b** and **Z-11b**

While the cross relation caused by the dipolar interaction between two nuclei leads to the observed NOE, dipolar interaction is not the only way in which nuclear relaxation can occur. Other mechanisms that cause relaxation are intermolecular interactions, unpaired electrons, electronic and magnetic instabilities of the instrument, and these relaxation mechanisms are the main reasons for reduced NOE values. As can be imagined, the experiment places considerable demands on the spectrometer, and consequently much folklore surrounds the NOE experiment. Some precautions can be taken to minimize these unwanted relaxation mechanisms. Intermolecular interactions can be minimized by dilution of the sample. The main source of unpaired electrons is dissolved oxygen in the sample, and oxygen can be removed by the freeze-pump-thaw degassing method¹⁰⁸ utilizing the Wilmad J. Young Valve NMR tube. Chemical shifts show significant temperature dependence, so careful monitoring of the temperature of the NMR instrument room is also necessary.

Consequently, the best time to do these experiments is in the early hours of the morning when the chance of somebody opening and closing the doors is smaller.

Since NOE enhancements depend upon the gradual building up of equilibrium populations, the presaturation of each signal should be carried out for at least three times (five times is preferable, but usually not feasible) the T_1 relaxation time for that proton. This requires a T_1 analysis for each of the signals to be irradiated. Typical relaxation rates of the vinyl protons of **11b** and **11c** for properly degassed samples were 7-8 s. The T_1 analysis also gives information about isolated protons, and protons that have unusually long relaxation times, as the vinylic protons do, suggest the relative isolation of these protons from other protons in the molecule. This is suggestive that the silyl enol ether isomer formed is the *Z* enol. The relative isolation of the vinyl proton was also confirmed by the fact that experimental modifications such as the highly touted cycloedof¹⁰⁹ (a cycled, difference spectrometry experiment) NMR experiments as well as the cruder, manual NMR NOE difference experiments failed to produce any NOE enhancements for **11b** or **11c**. Again, this result suggests, but does not prove, that the geometric structure for **11b** and **11c** is the *Z* isomer.

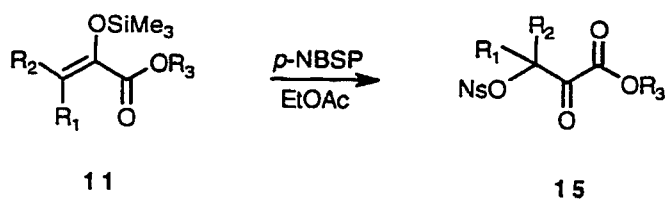
The NOE enhancement or the lack of it should not on its own be used for structure determination. Just as the observance of an NOE between two protons does not prove that the two protons are close, the lack of any NOE does not provide sufficient evidence that the two protons are far apart.¹¹⁰ Enhancements depend not only the interaction of the irradiated protons

because the total of all the of the other nearby unsaturated spins, and the total of all the of the other nearby unsaturated spins could be zero.¹¹⁰

Even though concrete evidence could not be obtained for the unambiguous stereochemical assignment of **11b** and **11c**, the stereochemistry assignment does not limit the use of silyl enol ethers as electron rich enol derivatives of α -keto esters. All of the required silyl enol ethers **11a-f** were prepared in good to excellent yields by one of two methods with the only major impurity, if any, being the α -keto ester. The reaction of **11a-f** with *p*-NBSP was examined, and *p*-NBSP was prepared by the condensation of (*p*-nitrophenyl)-sulfonyl chloride with hydrogen peroxide under alkaline conditions using a two phase reaction system at -78 ° C.⁷⁶ The resulting peroxide is a stable, white, crystalline solid that is handled safely in the laboratory with appropriate precautions.

Reaction of silyl enol ethers **11a-f** with *p*-NBSP in ethyl acetate at 0 °C (Equation 47) provided the desired 3-[[(*p*-nitrophenyl)sulfonyl]oxy] 2-keto esters **15a-f** in good yields (Table 5). The reaction was tolerant of a wide range of structures, although **15e,f** gave slightly lower yields. Products **15a,b,e-g** are solids that were purified by recrystallization, while **15c** is an oil and **15d** is a slushy oil. Purification of **15c** by chromatography worked quite nicely, and purification of **15d** was done by dissolving the oil in a minimum amount of ethyl acetate, adding hexane until cloudy, and collecting the resultant oil. All of the products can be stored for extended periods of time at 0 °C. Since silyl enol ethers, **11a-f**, occasionally contained some starting α -keto ester, a slight excess (10-15%) of **11a-f** was generally used to ensure

completion of reaction. Acceptable elemental analyses were obtained for all β -nosyloxy- α -keto esters **15a-g**.



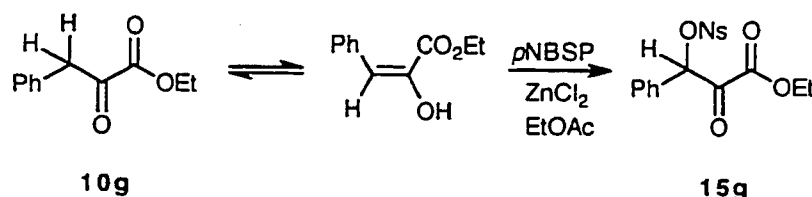
Equation 47

Table 5. Preparation of 3-[[(*p*-Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters

Product	R ₁	R ₂	R ₃	Yield (%)
15a	H	H	Me	82
15b	CH ₂ Ph	H	Et	82
15c	<i>n</i> -pentyl	H	Et	88
15d	CH ₃	EtOCO	Et	65
15e	CH ₃	CH ₃	Et	61
15f	-cyclohexyl-		Et	59
15g	Ph	H	Et	67

It was not necessary to prepare the silyl enol ether of ethyl 3-phenyl pyruvate, **10g**, because the enol content, as determined by ¹H NMR of the α -keto ester, was sufficient to sustain the bimolecular addition reaction with *p*NBSP in the presence of a Lewis acid, zinc chloride (Equation 48). Ethyl 3-(*p*-nitrobenzenesulfonyl)oxy]-3-phenyl-2-oxopropionate, **15g**, was obtained in

good yields. It has been reported^{95,96} that **10g** exists in two enol forms, the *E* and *Z*, as well as the ketone form. The amount of enol present appeared to dependent on the manner in which the α -keto ester was handled during preparation, since the enol content varied from 42% from one preparation to 84% in another trial.

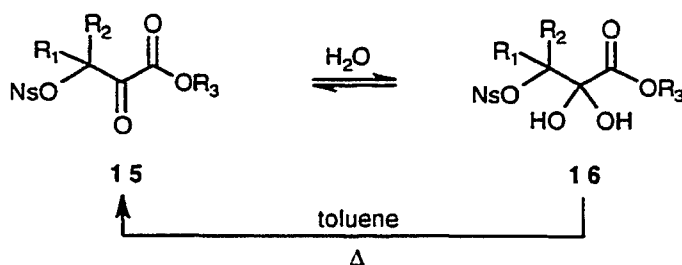


Equation 48

Another Lewis acid, boron trifluoride-diethyl etherate, was tried, but this modification provided less pure product than zinc chloride. The enol content of **10d** is also higher than normal. The reaction of **10d** with zinc chloride and *p*-NBSP was tried, but the enol content of **10d** was not sufficient to afford **15d** in good yields. The enol content as determined by ^1H NMR was 12% which led to the formation of about 20% of **12d**. It may be that the enolization is kinetically slow under the reaction conditions.

One interesting property of compounds **15a-g** is that slow hydration during storage occurs. Nosylates **15a** and **15b** hydrate the fastest while **15e** and **15f** show very little hydration even after prolonged storage. At first, this observation was viewed as a mere inconvenience, and the hydration was found to be reversible by heating the compounds to reflux in toluene with little degradation (Equation 49). Nosylate **15b** had to be routinely dehydrated in

this manner. Of all of the hydrated compounds, only ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2,2-dihydroxy-4-phenylbutanoate, **16b**, was actually isolated.



Equation 49

Hydrate **16b** was found to have a slightly higher melting point than the keto form, and it was only slightly soluble in CDCl_3 . While the complete ^1H NMR could be assigned in CDCl_3 solution, acetone- d_6 was required as the solvent for the ^{13}C NMR assignment of **16b**. In acetone- d_6 , nearly all of the chemical shifts for protons and carbons in **16b** were shifted relative to the unhydrated compound chemical shifts for **15b**, so the concentration of the two species could be easily calculated from the integration of the proton signals. Comparison of the ^{13}C NMR spectra of **15b** and **16b** showed the diagnostic loss of the ketone signal around 188 ppm and the identification of a new peak at 92 ppm, assigned as the gem diol carbon signal. The IR also shows the loss of the ketone stretch at 1724 cm^{-1} and the appearance of an O-H stretch at 3490 cm^{-1} . In addition, the ester stretch shifts from 1766 cm^{-1} in **15b** to 1736 cm^{-1} in **16b**.

Upon closer examination of the ^1H NMR spectra of the crude products **15a-g**, it was clear that some of the hydrated form was present after isolation; thus, hydration must be occurring during the aqueous work-up. While **15b** was hydrated to **16b** to the extent of 25%, ketonosylates **15a**, **15c**, and **15g** all contained about 10% of the carbonyl hydrate upon isolation (Table 6). More sterically hindered β -nosyloxy- α -keto esters show less hydration; **15d** showing less than 5% while **15e** and **15f** do not undergo appreciable hydration. The extent of hydration is probably an experimental artifact, which depends on the work-up procedure. For example, the amount of time that the product is exposed to aqueous conditions (i.e., extraction time) could be different for each individual reaction. The fact that fairly consistent amounts of hydration were obtained for each compound is indicative of the consistency of work-up, not to the establishment of equilibrium.

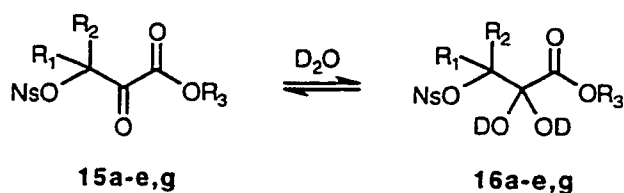
Table 6. Percent Hydration of 3-[[(*p*-Nitrophenyl)sulfonyl]oxy] 2-Keto Esters in CDCl_3 after Isolation

Product	R_1	R_2	R_3	Hydration (%)
16a	H	H	Me	10
16b	CH_2Ph	H	Et	24
16c	<i>n</i> -pentyl	H	Et	13
16d	CH_3	EtOCO	Et	<5
16e	CH_3	CH_3	Et	0
16f	-cyclohexyl-		Et	0
16g	Ph	H	Et	9

The fact that the hydration of **15a-g** was slow when the nosylates were stored in the solid form caused the importance of this phenomena to be under-estimated. The hydration reaction was not an issue in dry organic solvents, but the hydration could compete with other carbonyl additions in a water soluble solvent. In order to determine extent of hydration at equilibrium, and consequently learn more about the chemistry of the carbonyl group of 3-[[*p*-nitrophenyl]-sulfonyl]oxy] 2-keto esters, an equilibrium hydration of **15a-g** was carried out as a ^1H NMR study in acetone- d_6 containing water. The intent of these experiments was not to measure rates of hydration but to determine relative rates and positions of the hydration equilibria.

The experiments were done by taking a small amount (generally about 50 mg) of **15a-g** and dissolving it in dry acetone- d_6 . The ^1H and ^{13}C spectra were recorded for each compound. A few drops of D_2O was added (Equation 50), and the spectra was taken at various time intervals until no further change in concentrations could be detected as determined by the integration of the ^1H spectra. Examination of the data (Table 7), shows that **15a**, **15b**, and **15g** hydrate almost completely while **15c** and **15d** are 85% hydrated at equilibrium. In contrast, ionization (solvolysis) competes with hydration for the tertiary nosyloxy ketones **15e,f**. Hydration of **15e** is a faster process than ionization as evidenced by the fact **15e** is converted to **16e** (51%) after only 15 minutes, but decomposition has also begun. After 12 hours, **15e** has completely decomposed, and a mixture of unidentifiable products is obtained. No hydration for **15f** is seen at all, since no ^{13}C signal was detected in the region around 90-95 ppm (Equation 51), and only 38% conversion to the

solvolysis product, 17, is detected after 12 hours. Total decomposition of 15f has occurred after 48 hours.

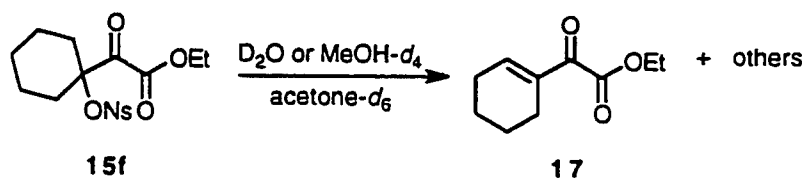


Equation 50

Table 7. Hydration of 3-[(*p*-Nitrophenyl)sulfonyl]oxy] 2-Keto Esters in acetone- d_6

Product	R ₁	R ₂	R ₃	Hydration (%)	Time (min.)	¹³ C gem diol
16a	H	H	Me	99	15	92.4
16b	CH ₂ Ph	H	Et	96	30	94.1
16c	<i>n</i> -pentyl	H	Et	86	240	94.2
16d	CH ₃	EtOCO	Et	84	120	92.2
16e	CH ₃	CH ₃	Et	60*	20	96.1
16f	-cyclohexyl-		Et	0		
16g	Ph	H	Et	97	45	94.5

*decomposition product begins to appear after 15 minutes



Equation 51

4.2 Reactions of 3-[[(*p*-Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters

The data clearly established that hydration of β -nosyloxy- α -keto esters in water containing solvents occurs fairly rapidly and could significantly compete with other carbonyl addition reactions. On the other hand, the hydration of the nosylates stored as solids at -20 °C was less than 10% and was reversible. Before any reaction of any of the 3-[[(*p*-nitrophenyl)-sulfonyl]oxy] 2-keto esters was attempted, a quick assay by ^1H NMR was done to determine extent of hydration. If necessary, **15a-g** were dehydrated in refluxing toluene. Nosylate **15b** required this treatment virtually every time while the other compounds rarely required the dehydration step. This facile hydration of 3-[[(*p*-nitrophenyl)-sulfonyl]oxy] 2-keto esters indicated that these compounds might have some interesting and unusual chemical characteristics. Leaving the ester group untouched, chemical manipulations of the nosylate group and the carbonyl group were envisioned.

The two general types of carbonyl chemistry are addition of a nucleophile to the carbonyl group and removal of a proton from the α -C (Figure 7). Both processes arise from the electron deficiency of the carbonyl group. Attachment of an electron withdrawing group (the nosyloxy group) vicinal to the carbonyl group further activates both of these processes. To manipulate the chemistry to one of pathways, balancing of the reactivity of the reagents and the carbonyl must be achieved. It was envisioned that the ketone group of β -nosyloxy- α -keto esters, **15**, would easily undergo reactions involving nucleophiles and bases. Besides the potential carbonyl chemistry,

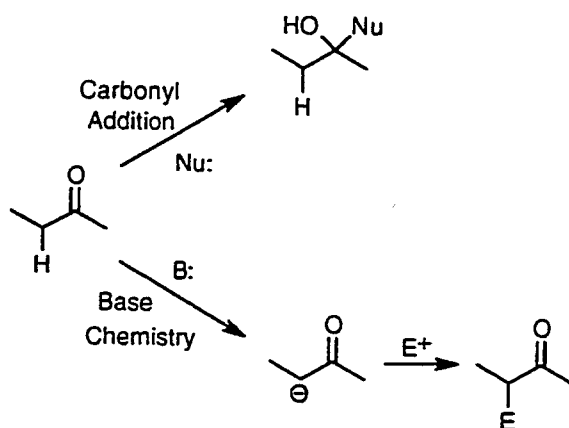


Figure 7. General Types of Carbonyl Chemistry

substitution reactions at the β C could also be envisioned due the excellent leaving group abilities of the nosylate group. Thus, these trifunctionalized compounds could potentially provide facile routes to other 1,2,3-trifunctionalized compounds by carbonyl chemistry and substitution processes without the need for undue protection schemes.

One interesting sequence of reactions would involve a comparison of the reduction-substitution sequence versus the substitution-reduction sequence (Figure 8). The two different chemical sequences could potentially provide the same end-product, a β -substituted- α -hydroxy ester, but the two products from the two sequences would be diastereomers of each other. This type of stereochemical control adds to the diversity of compounds accessible from β -nosyloxy- α -keto esters. The upper pathway (Figure 8) is the reduction-substitution sequence, and this pathway was attempted first.

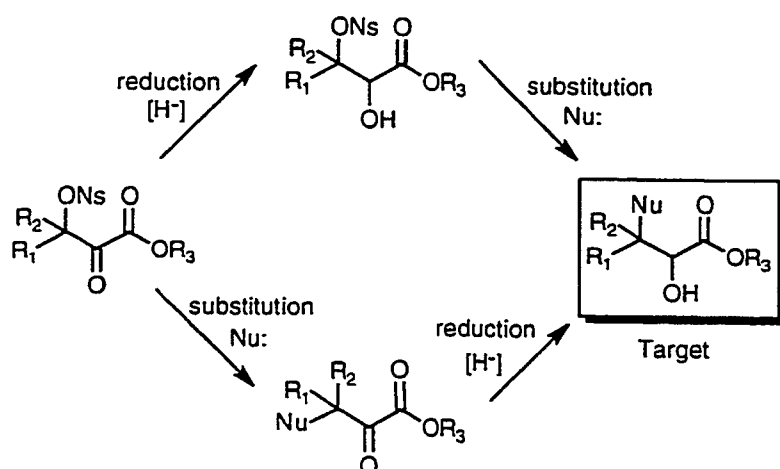
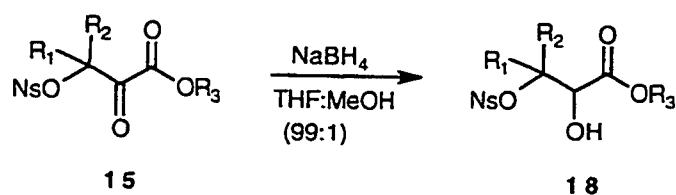


Figure 8. Reduction-Substitution and Substitution-Reduction Schemes

As discussed in the background, a very similar reaction sequence was seen in the reduction of 2-nosyloxy-3-keto esters in absolute ethanol at 0 °C (Equation 36) to give a ratio of *syn: anti* (2:1) of 3-hydroxy-2-nosyloxy esters. The success of the reduction of the 3-keto-2-nosyloxy esters prompted similar reaction conditions to be tried for **15b**, but only a pale yellow solid that polymerized after initial isolation was obtained. Examination of the literature provided modified procedures. Different solvents, such as methanol^{111,112,113} and methylene chloride,¹¹⁴ have been used with sodium borohydride, but the chosen procedure used a mixed solvent system of THF:MeOH (99:1) at -78 °C.¹¹⁵ These modified conditions were tried (Equation 52), and fair yields (Table 8) of methyl 3-[(*p*-nitrobenzenesulfonyl)-oxy]-2-hydroxy-propionate, **18a**, ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxy-4-phenylbutanoate, **18b**,

and ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxy-4-octanoate, **18c** were obtained.



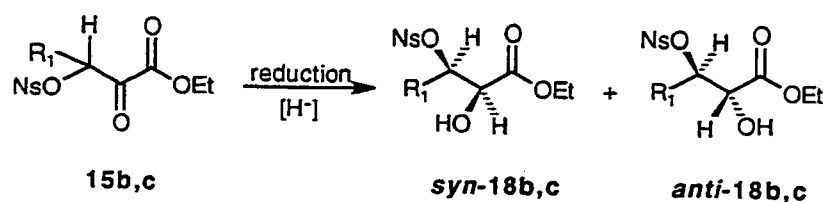
Equation 52

Table 8. Reduction of 3-[[(*p*-Nitrophenyl)-Sulfonyl]Oxy] 2-Keto Esters with Sodium Borohydride

Product	R ₁	R ₂	R ₃	Yield (%)
18a	H	H	Me	42
18b	CH ₂ Ph	H	Et	84
18c	<i>n</i> -pentyl	H	Et	62

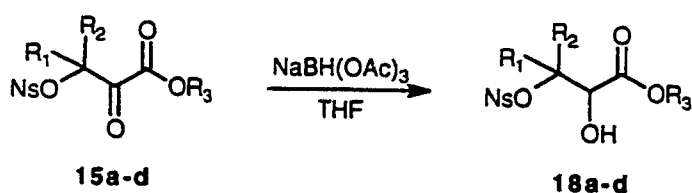
Reduction of **18b** and **18c** could provide two possible diastereomers, *syn* and *anti* (Equation 53). If no selectivity in the addition of the hydride to the carbonyl is observed, then equal amounts of the two diastereomers would be seen. If the hydride addition undergoes selective addition, then the other extreme is observed, complete stereospecific reduction with only one of the two diastereomers detected. Although not anticipated, only one of the two possible diastereomers of **18b** and **18c** was obtained. Even though the reaction provided stereoselective reduction of **15b** and **15c**, one problem with

this synthesis was the fact the products were difficult to separate from unidentified side-products. It appeared that overreduction of the ester might have also occurred. Since the yields were not high and the purification was trouble-some, a milder reducing agent was sought.



Equation 53

Of the many choices of mild reducing agents available, sodium triacetoxyborohydride was chosen.^{116,117,118} Reductions of **15a-d** using sodium triacetoxyborohydride in THF (Equation 54) provided crude products that were much easier to isolate from reaction mixtures, and the yields (Table 9) were improved for the reduction of **15a** and **15c**. Reactions were run at room temperature, generally overnight; colder reaction conditions (-78 °C) provided no reduction whatsoever. As with sodium borohydride, reduction of **15b** and **15c** gave only one set of the diastereomers, while reduction of **15d** afforded an almost equal, inseparable mixture of *syn* and *anti* diastereomers.

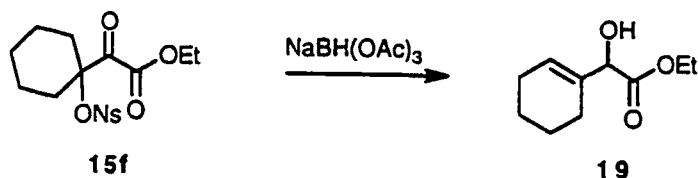


Equation 54

Table 9. Reduction of 3-[[(*p*-Nitrophenyl)-Sulfonyl]Oxy] 2-Keto Esters with Sodium Triacetoxyborohydride

Product	R ₁	R ₂	R ₃	Yield (%)	<i>syn:anti</i>
18a	H	H	Me	61	N/A
18b	CH ₂ Ph	H	Et	77	100:0
18c	<i>n</i> -pentyl	H	Et	70	100:0
18d	CH ₃	EtOCO	Et	81	55:45

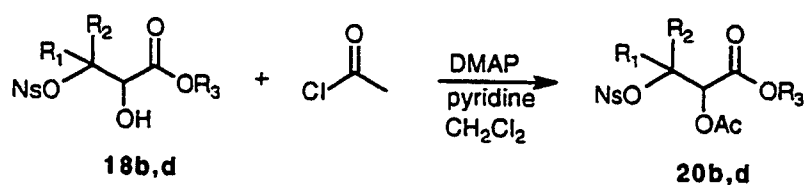
Although only small amounts of reduction products **18e-g** were isolated, reduction of the β -nosyloxy- α -keto esters, **15e-g**, by sodium triacetoxyborohydride must have occurred as evidenced by the decomposition products isolated for these reductions. For example, reaction of **15f** with sodium triacetoxyborohydride provided the cleanest reaction of these three, and the product isolated 2-carboethoxy-1-hydroxy-cyclohexene, **19**, arises from elimination as well as reduction (Equation 55). Reduction of **15e** gave a mixture of products including reduction product, **18e**, but reduction of **15g** appeared to produce self-condensation as evidenced by the large amount of phenyl protons in the ¹H NMR.



Equation 55

The reduced products **18a** and **18b** were stable, solids that could be purified by recrystallization. This was not the case for **18c** and **18d** which were collected as oils. Nosylates **18a-d** were not stable to silica gel chromatography, due to the potential ring closure of **18a-d** to give glycidic esters, **22**, so purification by this method was not feasible. Fortunately, both **18c** and **18d** could be purified by dissolving the crude mixture in a minimum of ethyl acetate, adding enough hexane to make the solution turn cloudy, and collecting the resulting oil. However, the diastereomers of **18d** were inseparable by this technique. In order to separate the **18d** diastereomers and also to investigate the possibility of enzymatic resolution of **18b** and **18c**, several hydroxyl protecting groups were investigated.

Conversion of the hydroxyl group of **18b** to the acetate ester with acetyl chloride¹¹⁹ in the presence of 4-dimethylaminopyridine, DMAP,¹²⁰ afforded ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-acetoxy-4-phenylbutanoate, **20b**, as a crystalline solid (Equation 56). Only one attempt at enzymatic resolution with porcine pancreatic lipase¹²¹ was made, but the resolution was unsuccessful. Acetylation of **18d** was achieved with similar results as **18b** to provide **20d** (Table 10). The acetylated diastereomers of **20d** were successfully separated by HPLC to afford the diastereomers with little loss of either diastereomer.



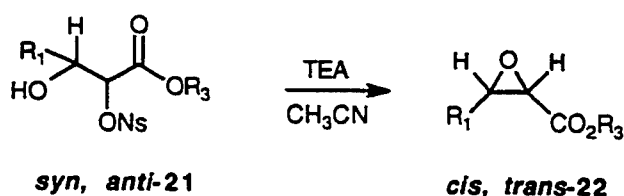
Equation 56

Table 10. Protection of 18b and 18d with Acetyl Chloride

Product	R ₁	R ₂	R ₃	Yield (%)
20b	CH ₂ Ph	H	Et	94
20d	CH ₃	EtOCO	Et	61

Protection of the hydroxyl group as an acetate ester facilitated the separation of **18d** since almost a 1:1 ratio of the *syn* and *anti* were produced. The question of which diastereomer, *syn* or *anti*, was formed in the diastereospecific reduction of **15b** and **15c** still remained. As discussed earlier, the diastereoselectivity of the reduction of **15b** and **15c** by sodium triacetoxyborohydride gave a single diastereomer of **18b** and **18c** (Equation 53). Even if both diastereomers had been produced, it is often difficult to *a priori* assign *syn* and *anti* by chemical shifts and/or coupling constants, since these values tend to vary in an unsystematic fashion.

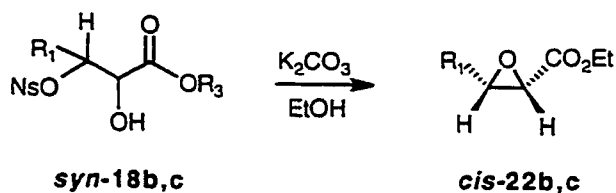
A similar problem was faced in the reduction of 3-keto-2-nosyloxy esters to 3-hydroxy-2-nosyloxy esters, **21**, discussed earlier (Equation 36),⁹¹ and in that case, intramolecular ring closing of **21** to provide *cis*-glycidic esters, **22**, was used to determine the diastereomer composition (Equation 57). The *cis* and the *trans* glycidic esters have unambiguous chemical shifts



Equation 57

and coupling constants of the C₂ proton, and these can be used to determine the stereochemical identity of the reduction products.

Ring closure of **18b** and **18c** to afford glycidic esters, **22**, was achieved by treatment with potassium carbonate⁶⁷ in absolute ethanol (Equation 58). Other reaction conditions^{52,91} have been utilized, but the above conditions were found to give the least epimerization. Therefore, **18b** and **18c** were dissolved in absolute ethanol and powdered potassium carbonate was added, and after purification by preparative thin layer chromatography, glycidic esters were obtained in good yields (Table 11). In both cases, the ¹H NMR spectral data was consistent with the coupling constants and chemical shifts of *cis* glycidic esters, so ring closure of **18b** and **18c** afforded *cis*-**22** (Equation 58). The spectral data for *trans*-**22b**⁴⁹ and *trans*-**22c**⁴⁴ have been reported, and the spectral data obtained for the ring closure of **18b** and **18c** does not match the spectral data reported for either of the *trans* isomers.

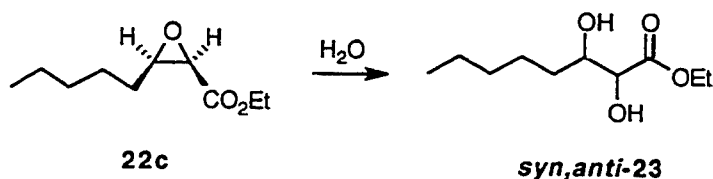


Equation 58

Table 11. Ring Closure of **18b** and **18c**

Product	R ₁	R ₂	Yield (%)	δ (J, Hz)
22b	CH ₂ Ph	H	77	3.58 (4.8)
22c	<i>n</i> -pentyl	H	45	3.52 (3.2)

Careful drying of the preparative thin layer chromatography plate was required, because it was found for **22c** that water adsorbed to the plate caused ring opening to give the 2,3-dihydroxy ester, **23** (Equation 59). Ring opening must have occurred with epimerization at C₂ and C₃, since **23** was isolated as a mixture of *syn* and *anti* diastereomers.



Equation 59

To confirm the *cis*-assignment of **22b** and **22c**, NOE experiments were done as previously described for the silyl enol ethers. These NOE experiments confirmed the *cis* geometry. The T_1 analysis for the C₂ protons for **22b** showed that this proton relaxed in less than 4 seconds when the sample was not deoxygenated and relaxed in 7 seconds after the sample was subjected to deoxygenation. To further test the necessity of deoxygenation, the manual NOE experiment was done without prior deoxygenation. No useful NOE enhancements were seen. The more sensitive cycledof NOE experiment showed small NOE's with the oxygenated sample. Deoxygenation appears to make a rather substantial difference. When the C₂ proton of **22b** was irradiated, the C₃ proton showed a 20% enhancement, and when the C₃ proton was irradiated the C₂ proton was enhanced by 29% (Figure 9). Similar results were found for **22c**.

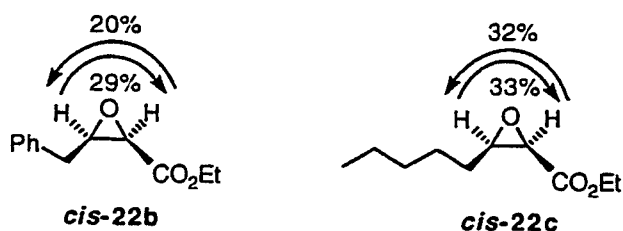
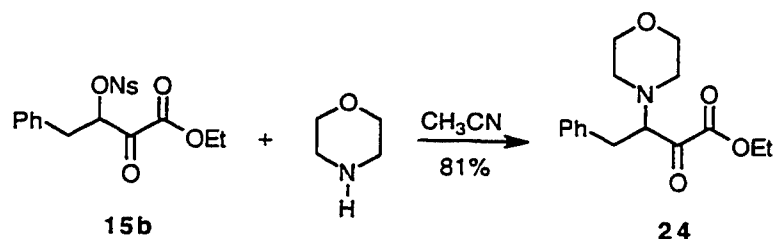


Figure 9. NOE Enhancements of *cis-22b* and *cis-22c*

The reductions of **15** with hydride reducing agents were more problematic than expected. Only when R_2 was a proton or a carboethoxy group did the reduction work well. The fact that β -nosyloxy- α -hydroxy esters, **18b** and **18c**, readily undergo ring closure with base suggests that further reactions of reduction products **18a-d** with basic nucleophiles would also give glycidic esters instead of substitution. The reduction-substitution scheme will not work as hoped (Figure 8), so the substitution-reduction sequence was investigated next.

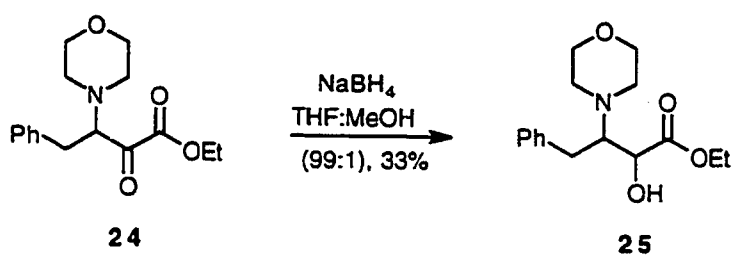
Since most common and dominant functional groups contain nitrogen, reactions of β -nosyloxy- α -keto esters with amine nucleophiles were tried. The reaction of **15b** with benzylamine and pyrrolidine only gave complex product mixtures; however, reaction of **15b** with morpholine gave an isolable product, ethyl 3-morpholino-3-phenyl-2-oxo-butanoate, **24**, in fairly good yields (Equation 60). Best results were obtained by dissolving **15b** in dry acetonitrile, adding morpholine, and allowing the mixture to stir for 12 hours at 0 °C. The product was not pure and was unstable to chromatography or any other type of purification process. Other 3-[[*p*-nitrophenyl]-sulfonyl]oxy 2-keto esters were tried. The reaction of **15g** with morpholine provided a

product with a strong stretch at 1636 cm^{-1} , but no ketone stretch was observed. The reaction of **15a** with morpholine immediately afforded a precipitate and a complex product mixture upon work-up.



Equation 60

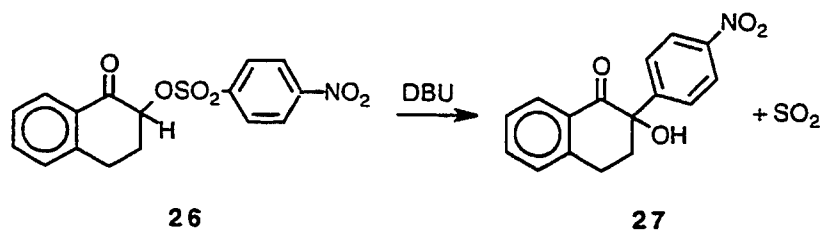
Since **24** couldn't be purified by normal methods, subsequent reduction with sodium borohydride gave a more stable product, ethyl 4-phenyl-3-morpholino-2-hydroxy butanoate, **25**, albeit in low yields (Equation 61). No attempts were made to optimize the yields of this reaction, since the substitution reaction had such limited scope.



Equation 61

Nucleophilic substitution of **15b** with amine nucleophiles appeared to be complicated by the competition of base promoted chemistry, so to

understand more about the carbonyl reactivity of the β -nosyloxy- α -keto esters, the base promoted chemistry was investigated. As previously discussed (Equation 31), α -nosyloxy ketones undergo base promoted chemistry with the non-nucleophilic base, 1,8-diazabicyclo[5.4.0]-undec-7-ene, DBU.⁸³ Treatment of α -nosyloxy ketones, **26**, with DBU (Equation 62) affords the α -hydroxy- α -*p*-(nitrophenyl) ketone, **27**.

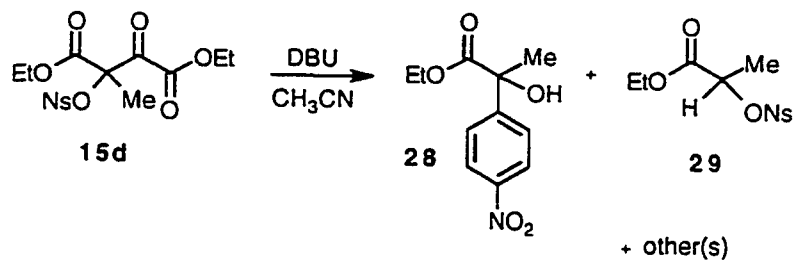


Equation 62

When **15b** was treated with DBU, the reaction immediately turned dark orange, a gas was evolved, and a complex product mixture was produced. It was thought that the gas evolved might contain carbon dioxide. Trapping the carbon dioxide with phenyl Grignard reagent would provide the corresponding benzoic acid. However, no carboxylic acid was detected upon hydrolytic work-up of the Grignard reagent.

One other 3-[[*p*-nitrophenyl]-sulfonyl]oxy 2- keto ester was reacted with DBU. The reaction of **15d** with DBU produced some interesting results. When DBU is added to a solution of **15d** in acetonitrile, the reaction turns yellow immediately with bubbles forming after 10 minutes, and after 2 hours, the amount of bubbles had slowed. The reaction was allowed to stir another 18 hours. Efforts to determine the identity of the gas by reaction with phenyl

Grignard reagent also failed. After aqueous work-up, two products were identified (Equation 63). As with the α -nosyloxy ketones,⁸³ the major product was the *ipso* substitution product, ethyl 2-hydroxy-2-(*p*-nitrophenyl)-propanoate, **28**, produced in 36% yield. The other compound identified in the by-product mixture was ethyl 2-[(*p*-nitrobenzenesulfonyl)oxy]propanoate,⁸⁰ **29**, isolated in 27% yield. The origins of **28** and **29** will be discussed later.



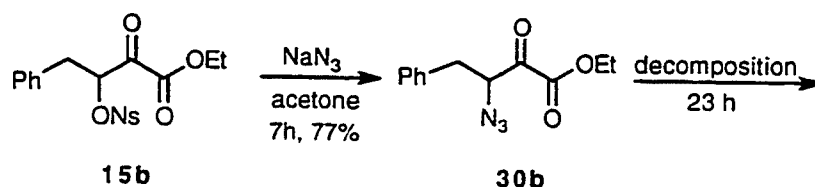
Equation 63

Although the base-promoted chemistry of **15d** with DBU gave very unusual rearrangement products, other examples of **15** gave intractable product mixtures with DBU. Moreover, it appeared that other amines which were employed as nucleophiles when reacted with **15b**, reacted as bases as well. Apparently, base-promoted decomposition of **15** is faster than nucleophilic substitution. Since the carbonyl reactivity of nosylate **15** was greater than expected, it was decided at this point to investigate the reactions of one of the 3-[(*p*-nitrophenyl)-sulfonyl]oxy 2-keto esters, **15b**, to discover what general chemical processes might be feasible and what other routes to 1,2,3-trifunctionalized products might be discovered.

Although limited success was achieved with amine nucleophiles, less basic amine equivalents could be used to continue the study of the substitution-reduction sequence (Figure 8). One particularly interesting amine-equivalent nucleophile is the azide ion. The azide ion can be easily reduced by hydrogenation, lithium aluminum hydride, and the Staudinger reaction to afford amines.¹²² Probably the most common synthesis of azides involves the nucleophilic substitution of halides by azide ion, typically in dimethylformamide and dimethylsulfoxide. Reaction of **15b** with sodium azide in dimethylsulfoxide provided a complex mixture of products. Recent reports from this laboratory,⁸⁴ utilized sodium azide in acetone to replace the nosylate group in simple α -nosyloxy ketones. Although the solubility of sodium azide in acetone is not as high as in dimethylsulfoxide or dimethylformamide, the concentration of azide ion is sufficiently high to provide substitution of the nosylate group. In addition, dimethylformamide and dimethylsulfoxide are often difficult solvents to remove; thus, a procedure using acetone as solvent has some definite experimental benefits. The reaction of **15b** with sodium azide in acetone was investigated.

The reaction of **15b** with sodium azide in acetone provided **16b**, the hydrated gem diol, as the only isolable product. Evidently, water present in the reaction mixture attacked the carbonyl faster than the azide ion displaced the nosylate. This result was a clear indication of how electrophilic the ketone carbonyl of **15b** was. Even though attack by water was faster, it was possible that azide ion could still undergo substitution of the nosylate group in the gem diol, **16b**. The reaction was repeated with **16b**, however, no substitution was observed after several days, presumably because the hydration product is

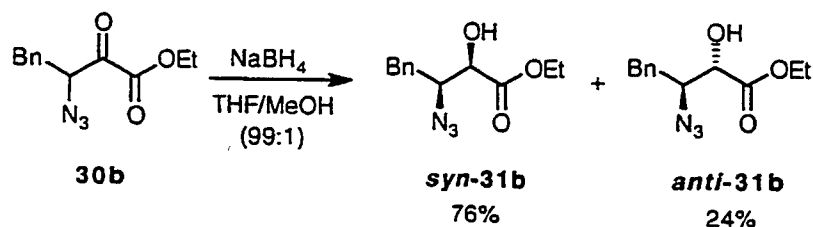
structurally is similar to a neopentyl nosylate, and the substitution would be sterically retarded. The acetone was scrupulously dried, and the reaction was repeated to provide 3-azido-2-oxo-4-phenyl butanoate, **30b**, in 77% yield (Equation 64).



Equation 64

The yields in the reaction of **15b** with azide ion in dry acetone were sometimes inconsistent, so a ^1H NMR experiment was used to monitor the course of the reaction. The reaction was repeated at $-78\text{ }^\circ\text{C}$, and after one hour, the ^1H NMR showed no reaction whatsoever. The reaction was allowed to warm to $0\text{ }^\circ\text{C}$ over an hour period, but the reaction was still sluggish. The reaction was allowed to gradually warm to room temperature during the next three hours. After a total of four hours, the product conversion was 53%, and after seven hours, there was 77% conversion to product. After eleven hours, no starting material remained, but the product was showing signs of decomposition. After twenty-three hours, virtually no product could be detected. From this experiment, it can be seen that **30b** is not very stable, but it could be used effectively without purification as a synthetic intermediate under the proper reaction conditions. Therefore, it appeared that azide ion was a viable alternative for the required nucleophilic amine equivalent in the substitution-reduction sequence (Figure 8).

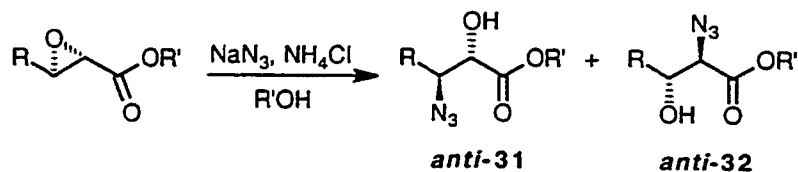
Once the chemical characteristics and experimental difficulties in the production of **30b** were determined, the reduction step in the substitution-reduction (Figure 8) sequence was carried out. Crude **30b** was prepared and was dissolved in THF:MeOH (99:1) at -78 °C, and sodium borohydride was added. The reduction of the carbonyl group worked well (90%) and ethyl 3-azido-2-hydroxy-4-phenylbutanoate, **31b**, as a mixture of *syn:anti* diastereomers in a ratio of 76%:24% was produced (Equation 65).



Equation 65

The assignment of *syn* and *anti* isomers was determined by comparison to the product obtained from the revised reduction-protection-substitution sequence (Figure 10) described later. Confirmation of the assignment of the diastereomers was obtained from the published results for the preparation of **anti-31b**.⁴⁹ As described earlier (Equation 16), ring opening of *trans*-glycidic esters with sodium azide provided a mixture of the two regioisomeric *anti*-3-azido-2-hydroxy esters, **anti-31**, and *anti*-3-hydroxy-2-azido-esters, **anti-32**, (Equation 66). The C_3 proton for **anti-31b** is reported to be buried under the quartet of the ethoxy methylene group at 3.9-4.3 ppm, and the signal for the C_2 proton is doublet at 3.7 ppm (no coupling constant reported).⁴⁹ In comparison, **syn-31b** prepared from the reduction of **30b**

(Equation 65), produced a ^1H NMR spectra with the C_3 proton as a multiplet at 3.72-3.81 ppm, and the signal for the C_2 proton was a doublet at 4.11 ppm ($J = 2.0$ Hz).



Equation 66

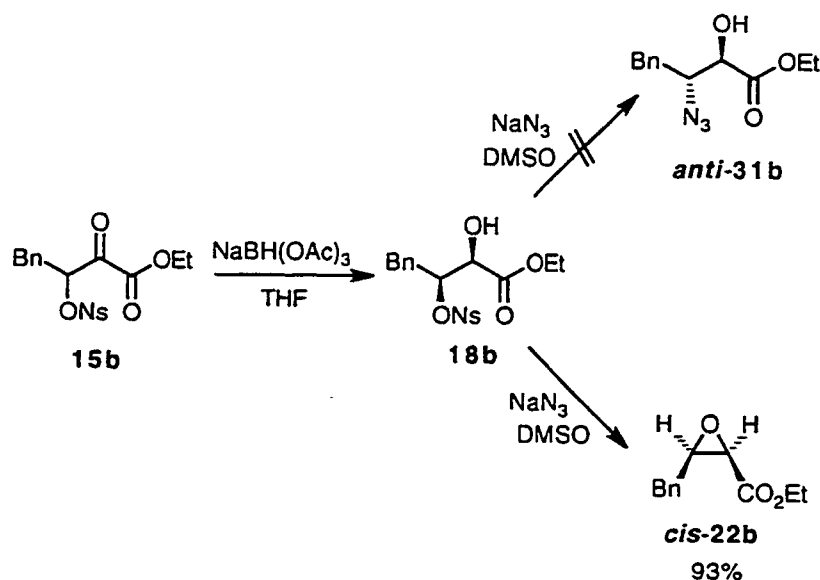
The ring opening reaction of other *trans*-glycidic esters with sodium azide has also been reported (Equation 66). If R was a phenyl group, then ring opening nucleophilic attack by azide occurs only at C_3 , and consequently, only **anti-31** was produced.⁴⁹ Since a mixture of the two regioisomeric products was not produced and R = Ph, the ^1H NMR spectra acquired for these compounds was greatly simplified. The coupling constants for the C_3 proton for the **anti-31** was found to be 4.5 Hz. In contrast, most reports for the azide ion ring opening of the *cis*-glycidic ester where R = Ph are for the preparation of taxol.^{51,52} The coupling constants found for (2*R*,3*S*)-(+)-methyl 3-azido-2-hydroxy-3-phenyl-propionate for the C_3 is 2.7 Hz. Therefore, when R = Ph, the C_3 coupling constant for the **anti-31** ($J = 4.5$ Hz) is much greater than the C_3 coupling constant for the **syn-31** ($J = 2.7$ Hz).

The same type of relationship between α -azido alcohols is found for **32**, the β -hydroxy- α -azido esters. More data has been acquired for this 1,2,3-trifunctional array. The *anti* isomer of **32** has been found to have coupling constants typically in the range of 5.6-6.4 Hz¹²³ and the *syn* isomer

of **32** have been reported to have coupling constants in the range of 3.8-4.0 Hz.^{123,124} For both regioisomers **31** and **32**, the coupling constant for the *anti* isomer appears to be larger than the coupling constant for the *syn* isomer. In summary, this preparation of 3-azido-2-hydroxy esters utilizes the substitution for nosylate by azide ion followed by reduction of the carbonyl group. This sequence, substitution-reduction sequence (Figure 8), provided the 3-azido-2-hydroxy esters in 62% overall yield in a *syn:anti* ratio of 74:26. For comparison, an alternate process for the production of 3-azido-2-hydroxy esters would use first, a reduction of the carbonyl group and then substitution of the nosylate by azide ion, a so-called reduction substitution sequence.

The first step in reduction-substitution sequence (Figure 8), the reduction of ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-4-phenyl butanoate, **15b**, provided exclusively *syn*-**18b**. As was stated earlier, it was thought that reaction of **18** with basic nitrogen containing nucleophiles, such as amines, would cause ring closure to glycidic esters, **22**. Therefore, it was anticipated that the substitution by the less basic azide ion would occur by a S_N2 process, and inversion at C₃ would provide *anti*-ethyl 3-azido-2-hydroxy-4-phenylbutanoate, *anti*-**31b**. A very similar type of manipulation was successfully used in the reaction of β -hydroxy- α -nosyloxy esters with sodium azide (Equation 38).⁹¹ Using traditional conditions for the substitution, *syn*-**18b** was dissolved in dimethyl-sulfoxide, and sodium azide was added. The reaction turned orange immediately, and the reaction was allowed to stir at 55 °C for 23 hours. After aqueous work-up, no substitution was obtained; the *cis* glycidic ester, *cis*-**22b**, was obtained in 93% yield (Equation 67). Even sodium azide was a sufficiently strong base to cause ring closure. In fact, the

yield and purity of the *cis*-22b was better than when ring closure was initiated with potassium carbonate was used.



Equation 67

There are two options for circumventing the ring closure. The first option would be to find another less basic amine-equivalent nucleophile. Since there are not many amine-equivalents less basic than azide ion, this is difficult. Therefore, the a second way to circumvent this problem is to protect the hydroxyl group of *syn*-18b. Unfortunately, the necessary protection step adds an additional two steps to the sequence (Figure 10), and the protection/deprotection steps contradict one of the original goals of this research. The reaction sequence has now become less efficient. However,

this transformation is required if the two reaction sequences are to be compared. Also, to complete the comparison, the same protection will be required of **31b**, so protection of the hydroxyl group of *syn*-**18b** and **31b** with ethyl chloroformate was investigated. The target compound, **34b**, obtained from the reduction-protection-substitution scheme will be labeled as **RPS**, and **34b** obtained from the substitution-reduction-protection scheme will be labeled as **SRP**.

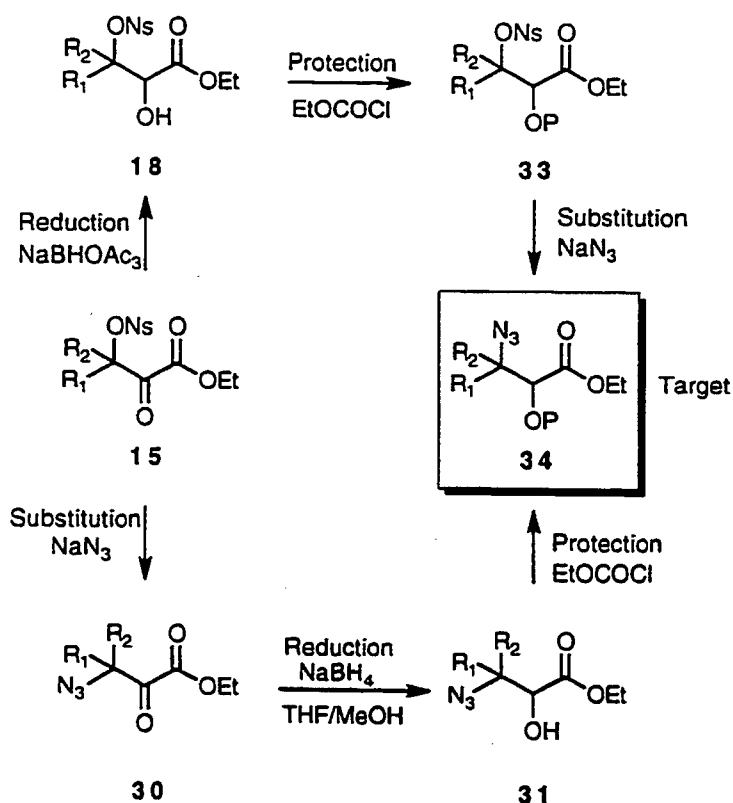
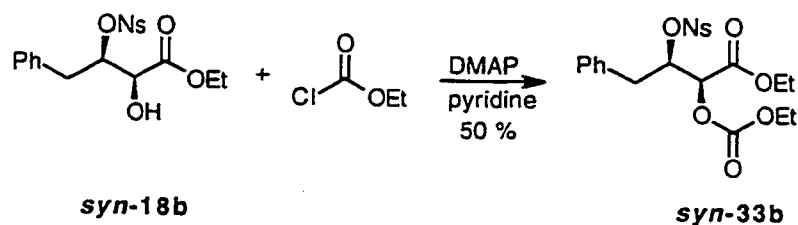


Figure 10. Revised Reduction and Substitution Schemes

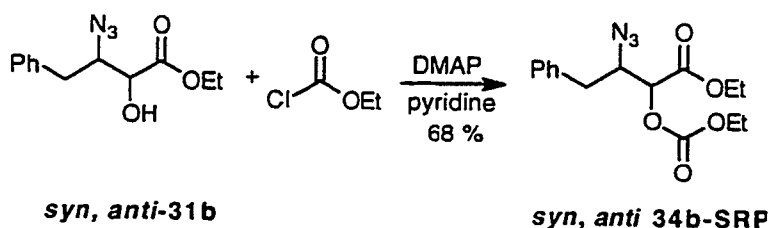
The protection of **syn-18b** with ethyl chloroformate was straightforward; **syn-18b** was dissolved in methylene chloride and ethyl chloroformate, DMAP, and pyridine were added (Equation 68). As before with the protection with acetyl chloride, best results were obtained from adding DMAP, and ethyl 3-[(*p*-nitrobenzenesulfonyl)]oxy]-2-carboethoxy-4-phenylbutanoate, **syn-33b**, was obtained as a crystalline solid in fair yields. The 50% yield reflects the yield of crystallized products, but the modest success of this reaction emphasizes the desire to avoid protection schemes when possible.



Equation 68

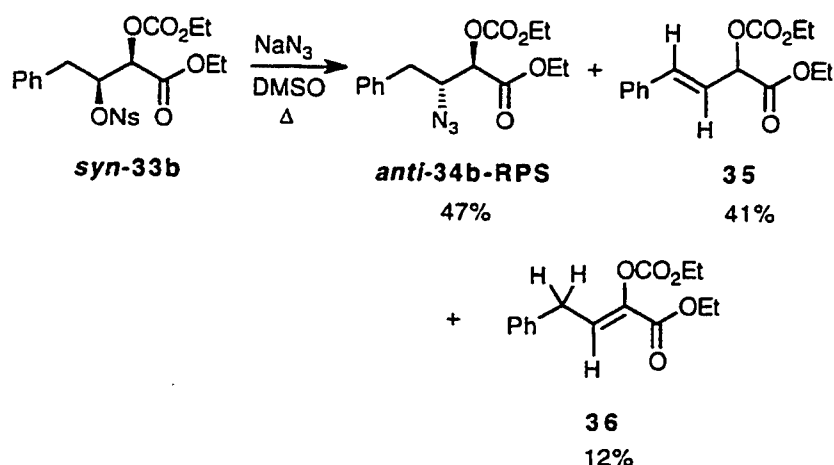
The same reaction conditions were utilized for the protection of ethyl 3-azido-2-hydroxy-4-phenyl butanoate, **31b**, with ethyl chloroformate. As was stated earlier, **31b** was obtained from the reduction of ethyl 3-azido-2-oxo-4-phenyl butanoate, **30b**, and sodium borohydride as a mixture of *syn* and *anti* diastereomers. Due to possible epimerization of C₂ and C₃, it was imperative that the protection scheme devised must not cause racemization of the diastereomers of **30b**. The NMR coupling constants and chemical shifts observed would be diagnostic in determining the identity of the major fraction when compared with **anti-34b-RPS** obtained from the reduction-protection-substitution sequence. Luckily, the conditions chosen provided ethyl 3-azido-

2-carboethoxy-4-phenylbutanoate, **34b-SRP** in 68% yield with retention of the *syn:anti* ratio, and no racemization was detected (Equation 69).



Equation 69

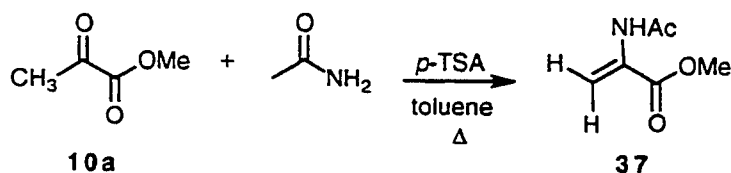
With the requisite *syn*-ethyl 3-[(*p*-nitrobenzenesulfonyl)]oxy]-2-carboethoxy-4-phenylbutanoate, **syn-33b**, in hand, the substitution reaction with sodium azide was investigated. When **syn-33b** was dissolved in dry acetone, no reaction at all was detected, so the reaction was repeated using DMSO at 60 °C overnight. After aqueous work-up, three products were isolated (Equation 70). The major fraction of the mixture (47%) was *anti*-ethyl 3-azido-2-carboethoxy-4-phenylbutanoate, **anti-34b**. Also isolated were the two, stereoisomeric elimination products ethyl 2-carboethoxy-3-ene-4-phenyl butyrate, **35**, isolated as 41% of the mixture, and ethyl 2-carboethoxy-2-ene-4-phenyl butyrate, **36**, isolated as 12% of the mixture. From the coupling constants for the alkene protons of **35**, it was deduced that **35** has *trans* geometry. Although, a good separation of the three products was not achieved even after purification by silica chromatography, the products are easily discernible by ¹H NMR, and total yields of each of the compounds based upon ¹H NMR integration in the purified mixture were **anti-34b-RPS** (29%), **35** (36%), **36** (12%).



Equation 70

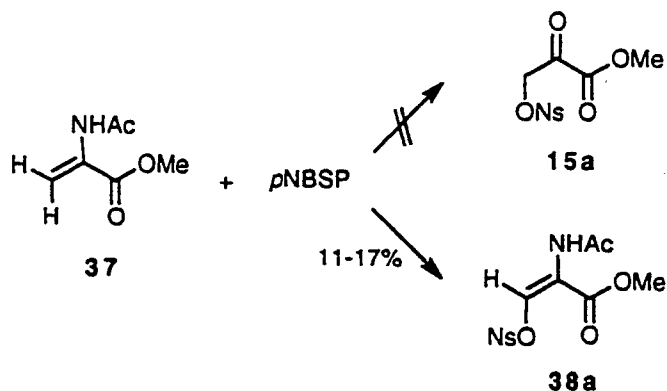
In summary, this preparation of 3-azido-2-carboethoxy esters utilizes the reduction-protection-substitution sequence (Figure 10). The total overall yield was not good and the extra protecting group step lowered the overall yield. In comparison, the substitution-reduction sequence did not require the extra protecting group and the protection was only done for the comparison of the reduction-protection-substitution sequence. Therefore, the substitution-reduction sequence is the better route to the β -azido- α -hydroxy esters. It had been hoped that the reduction-substitution sequence would have provided useful amounts of the *anti*- β -azido- α -hydroxy esters and the substitution-reduction sequence would have provided the *syn*- β -azido- α -hydroxy esters. This was not the case, since the β -nosyloxy- α -keto esters are base sensitive. A different approach to the similar types of products through neutral or acid catalyzed condensation reactions was considered.

Early results of a reaction of another enol derivative of α -keto ester, **10a**, with *p*-NBSP led to the notion that condensation reactions could be useful processes of β -nosyloxy- α -keto esters. The enol derivative used in this reaction was methyl 2-acetamido acrylate, **37**, and **37** was prepared by the condensation reaction of methyl pyruvate, **10a**, with acetamide (Equation 71).¹²⁵ Reaction of **37** with *p*-NBSP was predicted to afford **15a**, but only



Equation 71

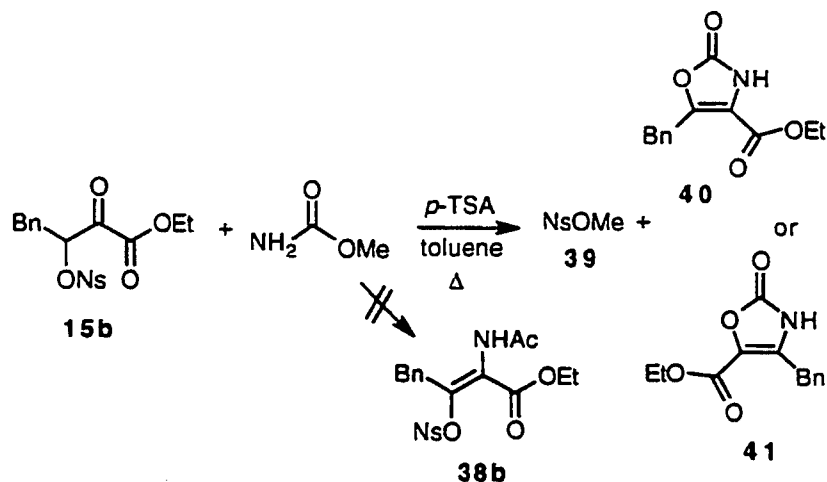
vinyl nosylate, **38a**, was isolated in low yields, 11-17% (Equation 72). Attempts to improve the yield of this reaction failed. The reaction was soon abandoned due to low yields of product and due to the preparation of other, more electron rich enol derivatives of α -keto esters.



Equation 72

What was surprising about this experiment was the unusual stability of **38a**. After aqueous work-up, **38a** was crystallized as a pale yellow solid with a fairly high melting point, and it could be stored for long periods of time without any sign of decomposition. If **38** could be obtained from another route, many unique transformations could be envisioned for **38**. Although azide ion had worked as an amine equivalent, the search for other substitution processes was continued. The properties of **38a** and the overall objectives of the research led to the idea of condensing nosylate, **15b**, with an amide nucleophile with the hope that structures like **38** could be accessed.

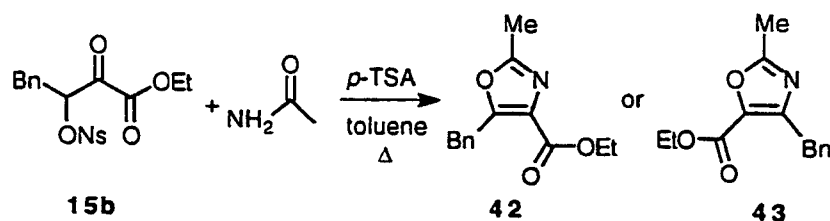
After initial dehydration of **15b** with toluene reflux, methyl carbamate and an acid catalyst, *p*-toluenesulfonic acid monohydrate, were added to the reflux apparatus. The reaction was allowed to reflux for 48 hours, and after aqueous work-up, the crude spectra showed what appeared to be the desired vinyl nosylate, **38b** (Equation 73). After careful fractionalization, the crude



Equation 73

mixture was separated into two components. Surprisingly, the first compound isolated was methyl 4-nitrobenzene sulfonate, **39**, whose spectra and physical properties matched an authentic sample. The other compound was determined to be an oxazolone, but not enough spectral data was obtained to distinguish between the two regioisomers 4-carboethoxy-5-benzyl-2-[3H] oxazolone, **40**, or 4-benzyl-5-carboethoxy-2-[3H] oxazolone, **41**.

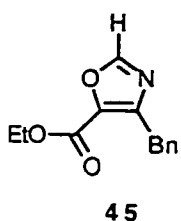
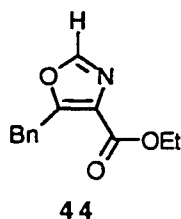
The amazing success of the reaction and the determination with methyl carbamate prompted work on the mechanism of the reaction. Another neutral nucleophile, acetamide, was utilized under the same reaction conditions, and another heterocycle, an oxazole, either 2-methyl-4-carboethoxy-5-benzyl oxazole, **42**, or 2-methyl-4-benzyl-5-carboethoxy oxazole, **43**, was obtained in good yields (Equation 74).



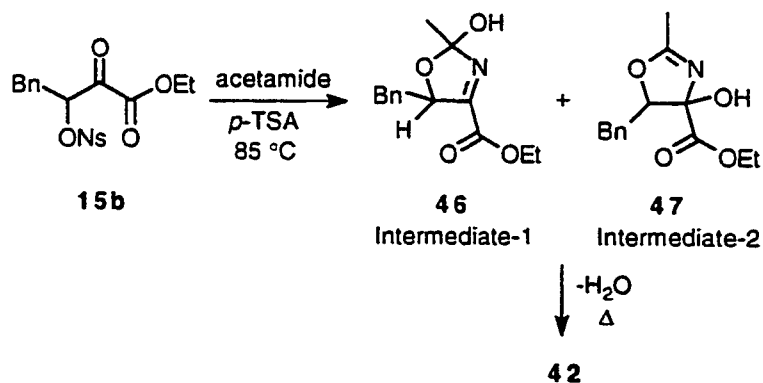
Equation 74

Examination of the literature¹²⁶ could not provide sufficient insight for discriminating between the two possible structures. Regioisomeric pairs of 4,5-disubstituted oxazoles were inadequately characterized^{127,128} to permit unambiguous identification of the oxazole structure. Only one compound, 4-carboethoxy-5-benzyl oxazole, **44**, was found to have a similar structure.¹²⁹ Unfortunately, its regioisomer, 4-benzyl-5-carboethoxy oxazole, **45**, has not

been synthesized nor characterized. The data for **42** was consistent with that for 4-carboethoxy-5-benzyl oxazole, **44**, but since the spectra for its regioisomer is not available, the structure assignment of **42** is tenuous.



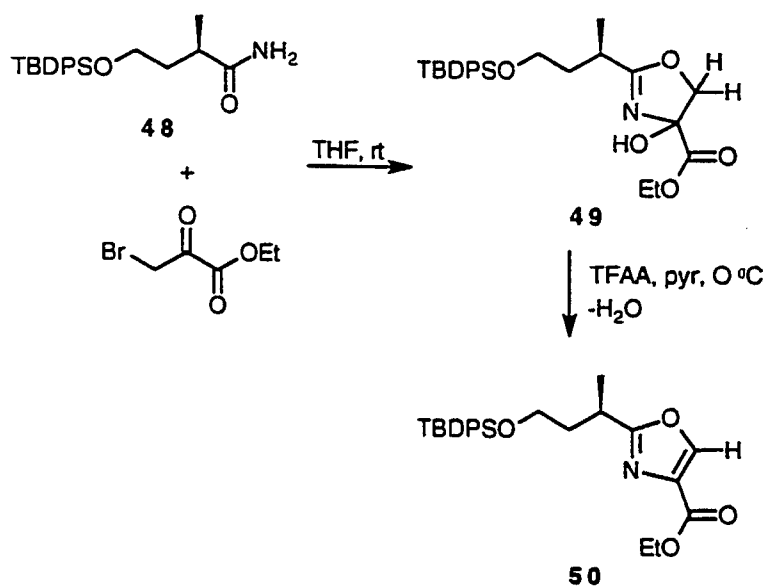
In the crude mixture, a small amount of a possible reaction intermediate was also detected, and it was hoped that the isolation and identification of this intermediate would allow positive identification of the oxazole regiochemistry. The reaction was repeated at lower temperatures and reduced times. When the reaction mixture was refluxed for four hours, there was 74% conversion to oxazole, and an intermediate was isolated in 13% yield (Equation 75). Heating for four hours at 85 °C, led to the isolation



Equation 75

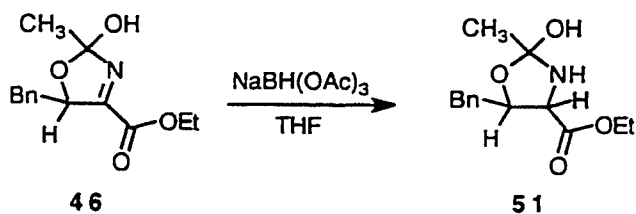
of the intermediate in 64% yield. The identity of the intermediate was tentatively assigned as 2-methyl-2-hydroxy-4-carboethoxy-5-benzyl-3-oxazoline, **46**. Also, a second intermediate was isolated in low yield and was tentatively assigned as 2-methyl-4-carboethoxy-4-hydroxy-5-benzyl-2-oxazoline, **47**.

Recently,¹³⁰ a similar reaction of ethyl bromopyruvate with an amide, **48**, was reported (Equation 76). It was claimed the intermediate, 4-hydroxyoxazoline, **49**, was formed, which upon dehydration afforded an oxazole, **50**. The 4-hydroxyoxazoline, **49**, described in that paper corresponds to intermediate-2, **47** (Equation 75), but no spectral data was reported that would substantiate this structural assignment.



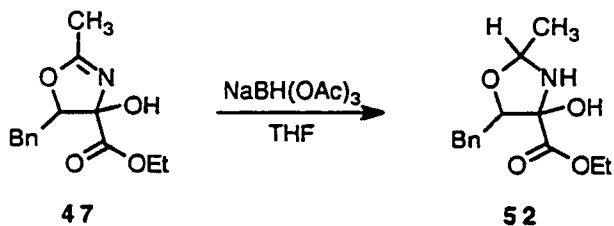
Equation 76

In order to assign structures for intermediates **46** and **47**, it was speculated that reduction of **46** would give 2-methyl-2-hydroxy-4-carboethoxy-5-benzyloxazolidine, **51** (Equation 77), whereas reduction of **47** would give 2-methyl-4-hydroxy-4-carboethoxy-5-benzyloxazolidine, **52** (Equation 78).



Equation 77

Compounds **51** and **52** can be differentiated easily by the ^1H NMR. Compound **51** should have the C_2 methyl signal as a singlet, whereas **52** should have the C_2 methyl split into a doublet by the C_2 proton (which should also be a quartet).

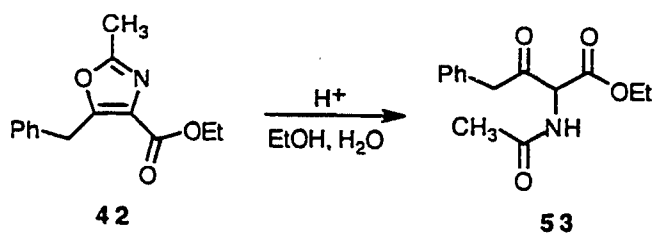


Equation 78

The reaction of **15b** with acetamide was repeated at $65\text{ }^\circ\text{C}$ for 18 h, and the ^1H NMR of the crude product showed almost complete formation of intermediate-1. The crude product, without further purification, was reduced

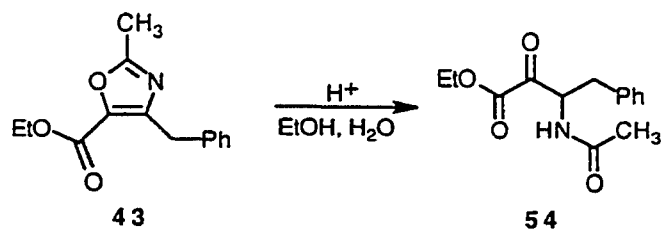
with sodium triacetoxyborohydride to give a product mixture that appeared to be composed of two sets of diastereomers. The data clearly show, however, the C₂ methyl signal to be a singlet. Therefore, the intermediate-1 must be structure **46** and not **47**.

In order to determine the regiochemistry of oxazole formation, acid catalyzed hydrolysis was investigated. The literature^{131,133,134} suggests hydrolytic ring cleavage of oxazoles can be accomplished by careful heating at 40-50 °C of the oxazole in a mixture of hydrochloric acid (3M) and ethanol. Prolonged heating or use of more concentrated hydrochloric acid (6M) and higher temperatures (90-95 °C) results in decarboxylation and α-amino ketone formation.^{131,134} If the oxazole product was **42**, then ring cleavage would afford the ethyl 2-acetamido-3-oxo-4-phenylbutanoate, **53** (Equation 79), and



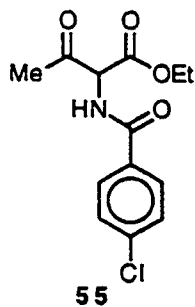
Equation 79

if the oxazole product was **43**, then ring cleavage would afford ethyl 3-acetamido-2-oxo-4-phenyl butanoate, **54** (Equation 80). Compound **53** and **54** are readily distinguishable by ¹H NMR, since the benzylic signal in **53** would be a singlet, while the benzylic signal in **54** would be part of an ABX spin system and produce a doublet of doublets for the diastereotopic protons.

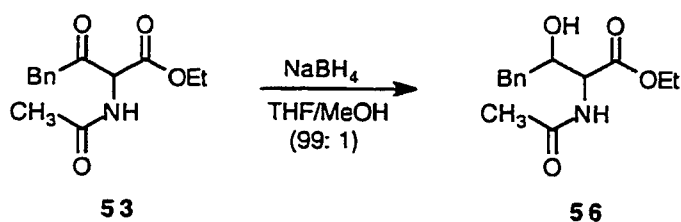


Equation 80

The ring cleavage reaction was carried out, and the ^1H NMR spectrum is consistent with the structure proposed for **53**. Although the unprotected ethyl 3-oxo-4-phenyl-2-amino-butanoate¹³¹ and the methyl 3-oxo-4-phenyl-2-amino-butanoate¹³³ are known compounds, **53** is an unknown compound. However, the ^1H NMR and IR spectrum matched the ring cleavage product of a similar compound, ethyl 2-(*p*-chloro)phenylcarbonyl-3-oxobutanoate, **55**.¹³⁵ The C_2 proton for **55** is a doublet at 5.42 δ , and the C_2 proton in **53** is 5.35 δ . The three carbonyl stretches in both compounds are also similar. The IR stretches for **55** are 1750, 1730, 1650 cm^{-1} , and the IR stretches for **53** are 1750, 1723, 1658 cm^{-1} . Therefore, the oxazole regioisomer prepared from the reaction of **15b** and acetamide must be 2-methyl-4-carboethoxy-5-benzyl oxazole, **42**.

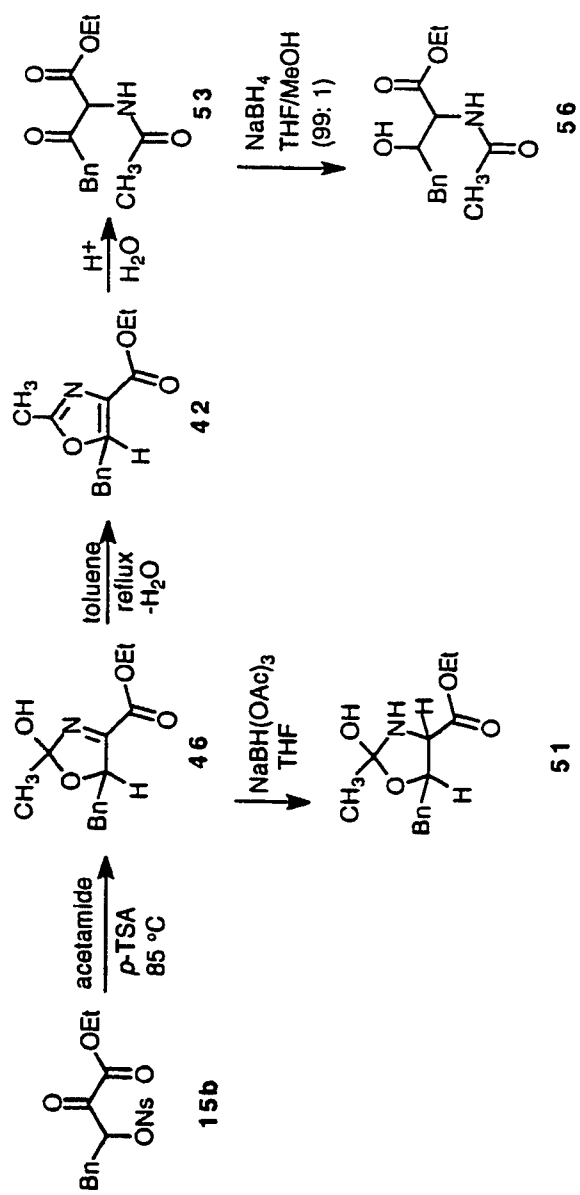


As additional structure proof, the ring cleavage product, **53** was reduced with sodium borohydride to give ethyl 2-acetamido-3-hydroxy-4-phenyl butanoate, **56**, (Equation 81). The reduction was attempted using sodium triacetoxyborohydride, but no reduction could be detected. This result further substantiates the assignment of the structure of the ring cleavage product to be **53**, since the activated carbonyl of **54** would have been reduced with the sodium triacetoxyborohydride.



Equation 81

In summary (Equation 82), the intermediate isolated from the acid catalyzed reaction of **15b** with acetamide was **46**, and the carbonyl of **46** was found to be electron deficient, since sodium triacetoxyborohydride, a mild reducing agent easily reduces **46** to afford **51**. If the reaction of **15b** with acetamide was heated to reflux with azeotropic removal of water, then oxazole **42** was obtained in good yields. The structure of **42** was confirmed by the acid catalyzed hydrolysis of **42** to afford β -keto- α -acetamido ester, **53**. The carbonyl of **53** cannot be reduced by sodium triacetoxyborohydride, but **53** did undergo reduction by sodium borohydride to afford a β -hydroxy- α -acetamido ester, **56**.



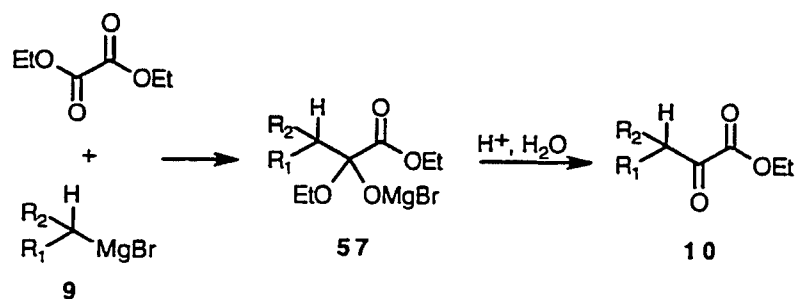
5. DISCUSSION

5.1 Preparation of 3-[[(*p*-Nitrophenyl)Sulfonyl]Oxy] 2-Keto Esters

The purpose of this research was to examine the synthetic utility of β -nosyloxy- α -keto esters as synthetic intermediates to other 1,2,3-trifunctionalized compounds. The project was divided into two phases. The first phase was the synthesis of β -nosyloxy- α -keto esters. The preparation of β -nosyloxy- α -keto esters required the electrophilic oxidative attachment of *p*-NBSP at the β -position of α -keto esters. Some α -keto esters, **10a-g**, were commercially available (Table 1). For α -keto esters that were not commercially available, the reaction of Grignard reagents, **9**, and diethyl oxalate was found to be the most expedient route to α -keto esters (Equation 41).⁹² The success of this general synthesis depended on the availability of the Grignard reagent, **9**, and the ability to separate the α -keto ester product, **10**, from diethyl oxalate.

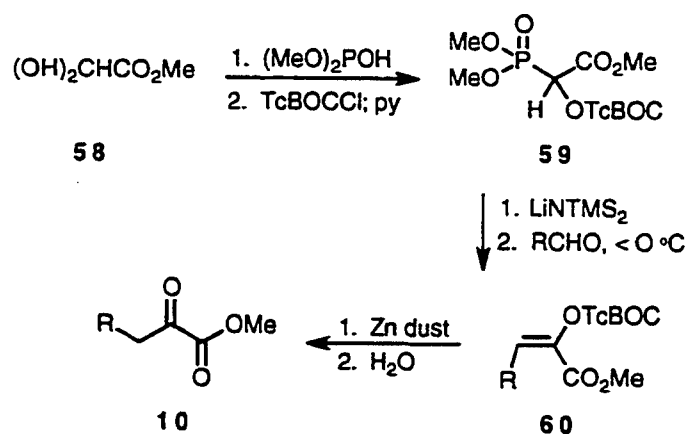
The reaction is believed to occur by nucleophilic addition of the Grignard reagent, **9**, to the diethyl oxalate to provide a tetrahedral intermediate, **57** (Equation 83).⁹³ The ketone group of the α -keto ester is only revealed upon hydrolysis, so only one equivalent of Grignard reagent adds to the ketone carbonyl. In contrast, unfunctionalized esters react with Grignard reagents to provide a tetrahedral adduct that collapses to give the ketone, and since the ketone is more reactive than the ester, another equivalent of Grignard reagent adds to afford the tertiary alcohol. If the ester has an electron withdrawing group attached, as in diethyl oxalate or ethyl trifluoroacetate,⁹⁷ the tetrahedral adduct is stabilized and collapse to the more

reactive ketone does not occur. In support of this mechanism, the initial tetrahedral adduct can be trapped with acetyl chloride.⁹⁷



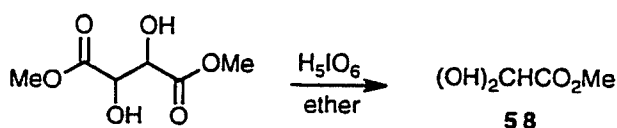
Equation 83

Another route to α -keto esters investigated briefly was a two carbon homologation of aldehydes (Equation 84) via a Horner-Emmons reaction.⁹⁸ In this multi-step sequence, methyl glyoxylate, **58**, is converted into a



Equation 84

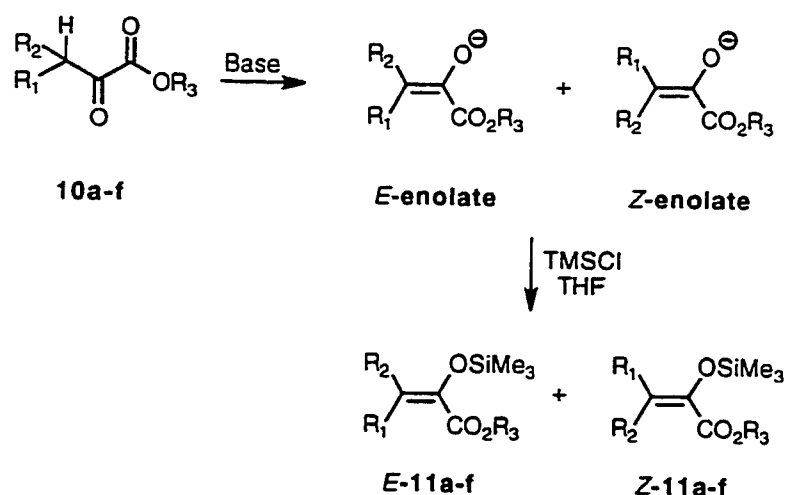
phosphonoglycolate ester, by treatment with dimethylphosphite. The hydroxyl group of the phosphonoglycolate is protected with trichloro-*t*-butoxy carbonate to give **59**, and the anion of **59** undergoes Horner-Emmons reaction with an aldehyde to produce the enol ether of the α -keto ester, **60**. Finally, the protecting group is removed by treatment with zinc dust, and hydrolysis provides the α -keto ester, **10**. The starting material, methyl glyoxylate, **58**, is prepared by cleavage of dimethyl tartrate with periodic acid (Equation 85).¹³⁶ In our hands, the cleavage of dimethyl tartrate failed to deliver methyl glyoxylate reliably, possibly due to overoxidation.



Equation 85

Other routes to α -keto esters not tried, but worth mentioning as possible alternative routes are oxidation of α -hydroxy esters,⁵⁹ reaction of organocadmium reagents with ethyl cyanoformate,⁹⁴ oxidative hydrolysis of 1,3-dithiane using NBS,⁹⁵ osmium tetroxide catalyzed oxidation of trimethylsilyl acetylenes,¹³⁷ and acid-catalyzed cleavage of α -acetyl amino- α -methoxy esters and α -imino esters¹³⁸ which are derived from readily available amino acids. Of these methods, the oxidation of α -hydroxy esters is probably the most straight-forward and highest-yielding preparation of α -keto esters. The only limitation to the oxidation method is the availability of the requisite α -hydroxy ester, but hundreds of the α -hydroxy acids are commercially available.

With the α -keto esters prepared, the carbon framework of the β -nosyloxy- α -keto esters was established, and the oxidation of the β -position of the α -keto ester could be examined. Since *p*-NBSP is an electrophilic oxidizing agent, the α -keto ester must function as a nucleophile, but α -keto esters are inherently electrophilic. Therefore, the reactivity of the α -keto ester had to be altered, and this was achieved by the transformation of the α -keto ester into the electron rich enol derivative. Two procedures were used to convert **10a-f** into the corresponding silyl enol ethers, which differed with respect to the base required for proton removal (Equation 86).

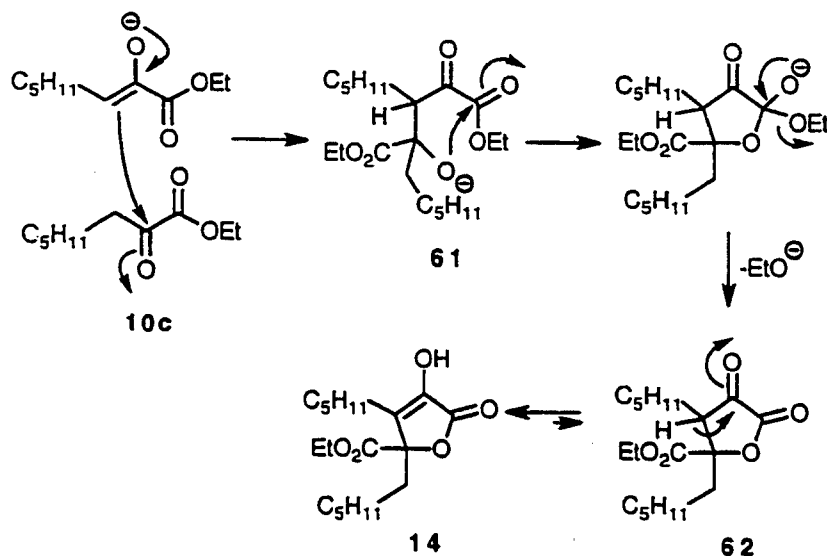


Equation 86

A structure dependent selection of the procedure was required. When R_2 was a proton or carboethoxy group, then utilization of triethylamine/chlorotrimethylsilane method provided the silyl enol ethers in good to excellent

yields (Table 2). Unfortunately, the triethylamine/chlorotrimethylsilane method failed to deliver product in productive yields when both R_1 and R_2 are alkyl groups. In these cases it was necessary to generate the enolate with potassium hydride and trap it with chlorotrimethylsilane. This procedure was effective for the preparation of **11e,f** (Table 4).

Attempts to develop a single general procedure for the preparation of trimethylsilyl enol ethers from α -keto esters were unsuccessful. As mentioned above, the triethylamine and chlorotrimethylsilane procedure does not succeed when R_1 and R_2 are both alkyl groups. Extension of the potassium hydride and chlorotrimethylsilane procedure to compounds where R_2 is a proton (**10c** was tried) failed as well because of self-condensation (Equation 87). Interestingly, the reaction does not stop at the β -alkoxy ester, **61**.



Equation 87

Intramolecular attack by the alkoxide oxygen on the ester displaces ethoxide to give a lactone, **62**, and **62** tautomerizes to the enol form, **14**. Thus, the methods used to convert α -keto esters to the silyl enol ether derivatives are effective but must be selected to match the structure of the starting material.

As previously shown (Equation 86), when the two R groups are not alike, as in **11b** and **11c**, then both of the *Z* and *E* isomers of the silyl enol ether are possible. Unexpectedly, only a single stereoisomer, the *Z* isomer, was produced in the reaction of **10b** and **10c** with triethylamine and chlorotrimethylsilane. The stereoselectivity can be explained by the examination of the conformations of the α -keto ester and transition states leading to enolate formation. The dihedral angle between the two carbonyl groups in the α -keto ester is affected by their dipole moments and the steric bulk of the R groups attached to the ester and ketone. From IR and dipole measurements, it has been determined¹³⁹ that the most stable conformation of an α -keto ester is that which has a dihedral angle between the two carbonyls of between 90 and 160°.

With the dihedral angle between the two carbonyl groups restricted to 90 and 160°, the transition state leading to enolate formation can be seen as a planar structure where the base removes the proton perpendicular to the plane of the carbonyl bond (Figure 11).¹⁴⁰ When R_1 is not the same as R_2 , there are two possible conformations A and B. Using the Cahn-Ingold-Prelog nomenclature, $R_1 > R_2$, the *Z* enolate results from conformation A, and conformation B leads to the *E* enolate. The two conformations differ in the orientation of R_1 and R_2 with respect to the esters group. The favored

conformation will depend upon the relative size difference of R_1 and R_2 and the interaction of the ester group with R_1 and R_2 .

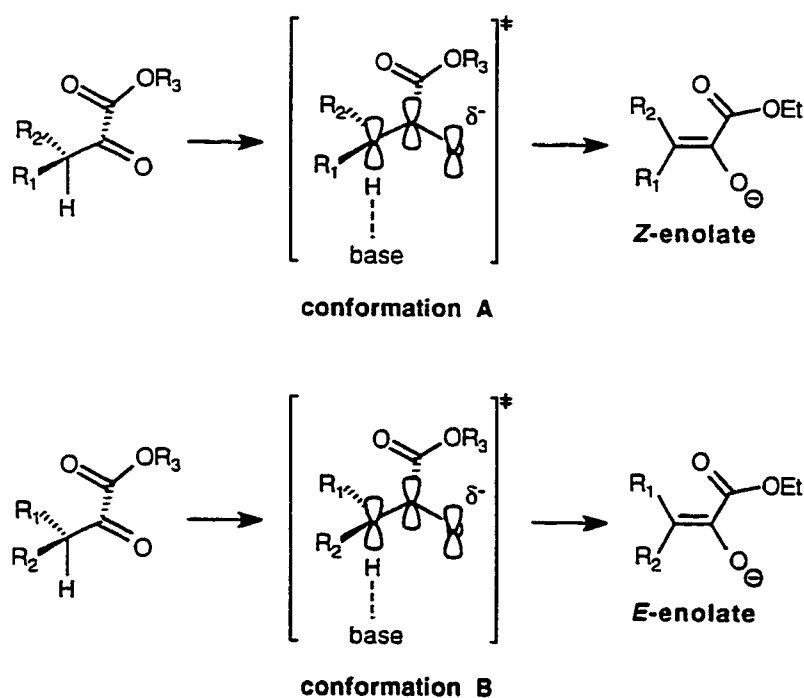


Figure 11. Conformations Leading to *cis* and *trans* Enolates of 10b,c

While the geometry of the double bond is more easily seen (Figure 11), the two conformations, A and B, and their respective transition states that lead to the enolates are most easily seen by a Newman projection (Figure 12). The lowest energy conformations are those in which the C-O bond is eclipsed by either a C-C or a C-H bond.¹⁰⁶ In conformation A, the C-O bond is shown eclipsed by R_1 , and in conformation B, the C-O bond is eclipsed by

R_2 . The gauche interaction between the carboethoxy group and the R group, either R_1 or R_2 , is key to understanding the stereoselectivity of the reaction. If $R_1 \gg R_2$, then the interaction of the carboethoxy group is smaller with R_2 . Therefore, conformer A is much more stable than conformer B, and the *Z* enolate will be preferentially formed.

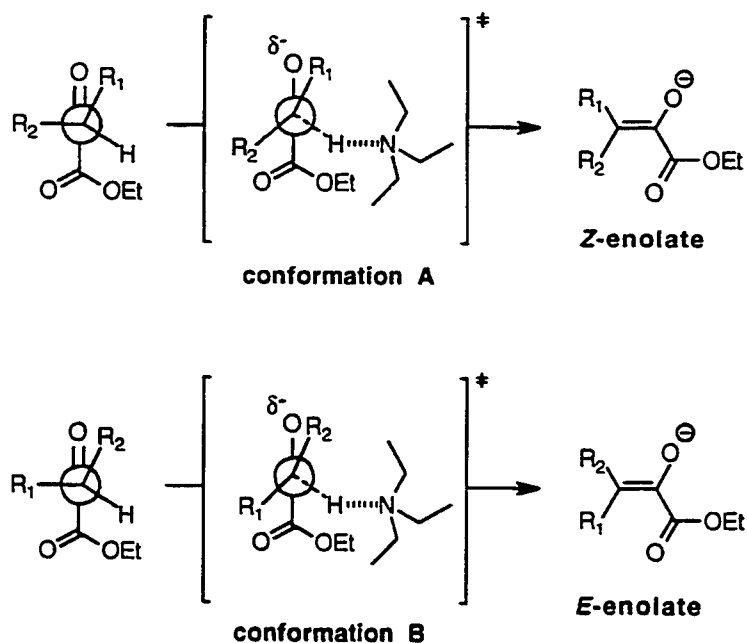
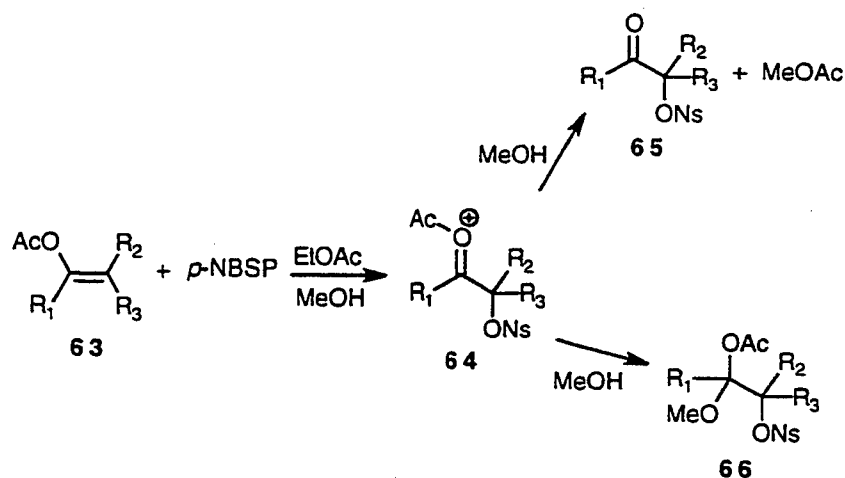


Figure 12. Newman Projections of Conformation A and Conformation B

With a source of trimethylsilyl enol ethers of α -keto esters developed, their conversion to β -nosyloxy- α -keto esters was carried out. Silyl enol ethers, enol acetates, enamines are all thought to react with *p*NBSP by electrophilic attack of *p*NBSP on the electron rich carbon-carbon double

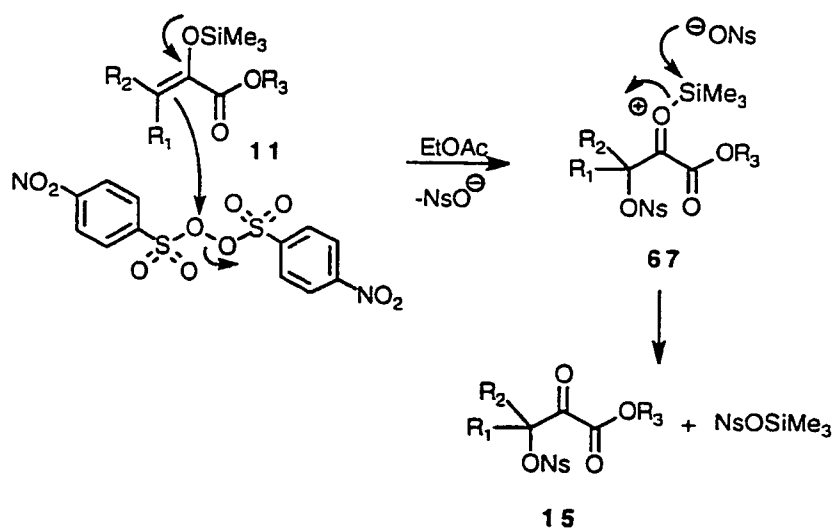
bond.⁷⁶ For example, reaction of *p*-NBSP with enol acetates, **63**, gave oxonium ion, **64**. Methanol, in the reaction mixture, traps **64** to afford α -nosyloxy ketones, **65** (Equation 88). Methanol was not found to undergo carbonyl addition to give **66**.⁷⁸



Equation 88

Assuming a similar type of mechanism for the reaction of *p*-NBSP with **11a-f**, the oxonium ion, **67**, would also be formed (Equation 89). Previous work suggested that methanol (or some other alcohol) was required for the success of the reaction;^{79,80} for the reaction of *p*-NBSP with **11a-f**, methanol was determined to be unnecessary. It is likely that in these systems the intermediate oxonium ion, **67**, is much more electrophilic and reacts with the nosylate counterion to generate the ketone directly. Regardless of the intermediate, the reaction of trimethylsilyl enol ethers with **11a-f** with *p*-NBSP

provides an effective preparation of β -nosyloxy- α -keto esters **15a-f** in good yields, and **15a-f** can be easily purified and stored in the freezer without degradation.



Equation 89

As was previously discussed (Equation 48),⁷⁹ **10g** had sufficiently high enol content to react directly with the *p*NBSP in good yields. Zinc chloride was found to be an effective catalyst for this process, and it has been postulated that zinc chloride to aid in the reaction mechanism by coordinating with oxygens of the *p*NBSP (Figure 13).¹²³ The coordination of the zinc ion contributes to the success of the reaction in two ways. First, the solubility of the *p*NBSP is increased, and consequently, the concentration of *p*-NBSP in solution is increased. Second, the complexation of *p*-NBSP with the zinc ion

enhances the electrophilicity of the *p*-NBSP, so electrophilic addition of the double bond to the *p*-NBSP is faster at lower temperatures. The same type of effect may also be occurring in this situation of the reaction of **10g** with *p*-NBSP. What is clear, is that the enol content of the α -keto ester needs to be greater than 25% to insure that the bimolecular reaction of the enol with the *p*NBSP is faster than the competing decomposition reactions of *p*NBSP.

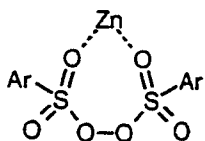


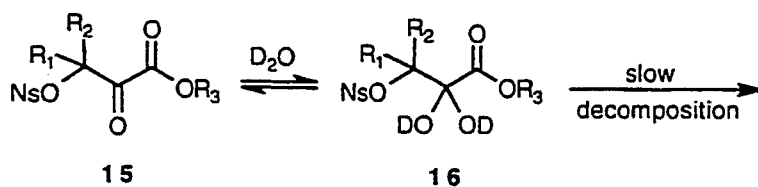
Figure 13. Complexation of *p*-NBSP with Zn^{+2}

None of the β -nosyloxy- α -keto esters were found to exist in the enol form. No extra peaks in the vinylic region in the ^1H NMR of **15a-g** were observed, and only two carbonyls absorptions corresponding to the ketone and the ester were seen in the IR spectra. This result is somewhat surprising especially for **15g**, since the parent α -keto ester **10g** has such high enol content. It is evident that attachment of a β -nosyloxy group destabilizes the enol form, as indicated by the **10g**, **11g** pair. This same preference for the keto tautomer was found for the isomeric β -keto- α -nosyloxy esters,⁸⁷ although the enol content of α -keto esters is generally lower than the enol content of β -keto esters studied earlier. While an electron withdrawing group at the α -position of a β -keto ester usually increases enolization, the lack of enolization of β -keto- α -nosyloxy esters was explained by the ability of the nosyloxy group to donate electron density by resonance into the unsaturated system thereby

destabilizing the enol form.⁸⁷ It is possible that the same electron donation by resonance at the β -position suppresses enol formation in β -nosyloxy- α -keto esters.

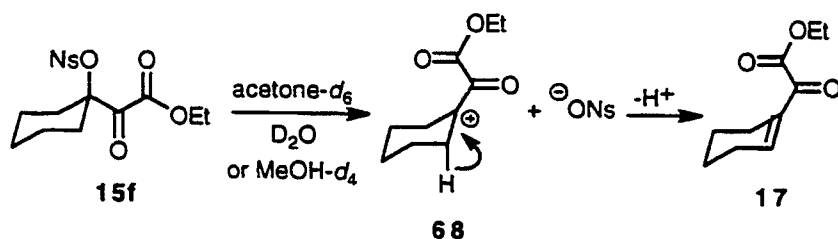
Although **15a-g** do not exist appreciably in the enol tautomer form, in contrast to other α -nosyloxy carbonyls prepared,⁷⁶ most of these nosyloxy ketones do hydrate to give gem diols **16a-d,g**. The susceptibility of **15a-d,g** (Equation 49) to undergo hydration to **16a-d,g** was not predicted to be an important consideration at the beginning of the project. The significance of the hydration was underestimated because only a small proportion of **15a-d,g** was actually hydrated during the work-up to the **16a-d,g**, the gem diol. Moreover, the hydration of solid samples of **15a-d,g** stored in the freezer was very slow. Obviously, the addition of water to the carbonyl group could compete with other carbonyl group addition reactions and could affect substitution reactions at C₃ of the β -nosyloxy group as well.

To determine how much the hydration might interfere with other carbonyl additions, a NMR hydration study of **15a-g** was done in acetone-*d*₆ with added D₂O. It was found that hydration was rapid, especially for **15a-d,g**, the least sterically crowded substrates (Equation 90). This result is consistent with other reports that have found hydrate formation in general to be more affected by steric effects than electronic effects.¹⁴¹ In all cases, the hydration of the carbonyl groups to the gem diol is followed by slow solvolytic decomposition. Since it is likely that there are small amounts of *p*-nitro-benzenesulfonic acid present, the decomposition could perhaps be acid catalyzed, but this is speculative.



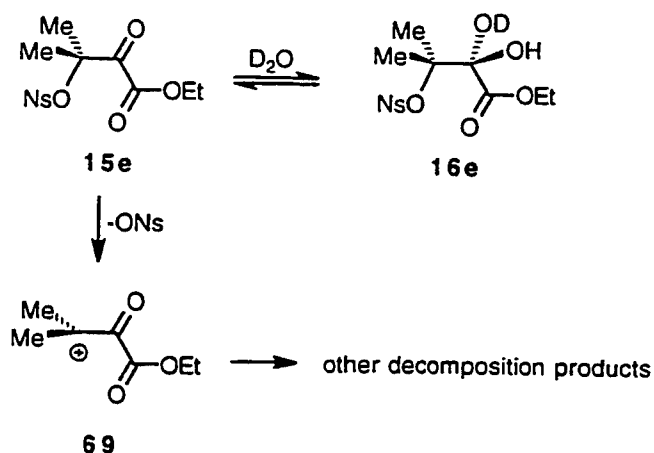
Equation 90

Hydration is not observed for tertiary nosylate **15f**, since hydration is sterically slowed to the point that ionization of the nosylate group is the faster process. However, even the ionization is a relatively slow process, since after 12 hours, only 38% of **15f** has undergone elimination to provide **17** (Equation 91). Compound **17** was clearly identified by examination of ^1H and the ^{13}C NMR spectra taken of the decomposing solution of **15f**. After 48 hours, **15f** had completely decomposed, and no identifiable products were found. Since **15f** is a tertiary nosylate, it is assumed that ionization to the tertiary carbocation, **68**, takes place, and it is probable that loss of the nosyloxy group is dependent on the polar, protic solvent mixture used for the hydration studies.



Equation 91

Unlike, **15f**, tertiary nosylate **15e** undergoes both hydration and ionization (Equation 92). Hydration is slightly faster than ionization, and only the hydration product, **16e** (51%), is seen after 15 minutes. Soon after, however, evidence of product decomposition is apparent, and complete decomposition is found after 12 hours. None of the decomposition products were identified, but by analogy to **15f**, it is assumed that ionization has occurred to afford a tertiary carbocation, **69**, that undergoes subsequent transformations.



Equation 92

Only recently have studies¹⁴² of the hydration susceptibility of other electrophilic ketones been examined. For example, it has been demonstrated that β -amino- α -keto esters,^{12,30} peptidyl fluoromethyl ketones⁵⁷ and fluoro ketones,^{143,144} β -fluoro- α -keto esters¹⁴⁴ all are readily hydrated in aqueous systems. These electrophilic carbonyl compounds have been prepared and

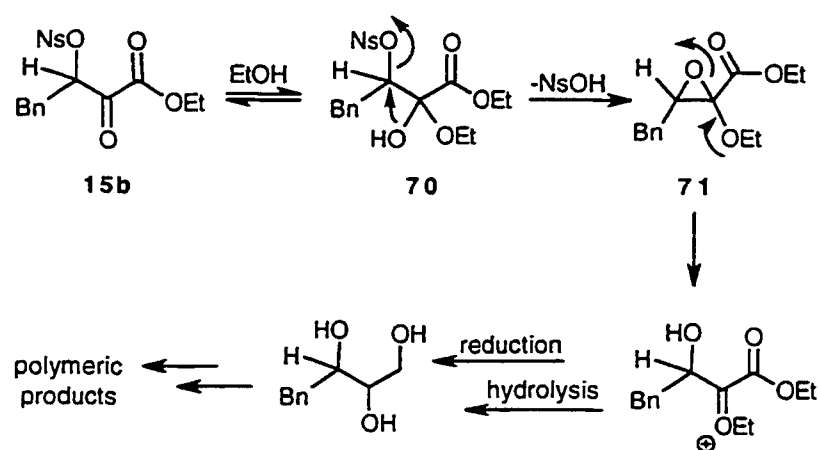
tested as potential proteinase inhibitors. While β -nosyloxy- α -keto esters **15** are not expected to be potential proteinase inhibitors, the position of the hydration equilibrium could prove useful for comparison with other electrophilic carbonyl compounds prepared in the future. The relatively fast rate of hydration of **15a-g** indicated that the carbonyl group of β -nosyloxy- α -keto esters of **15a-g** should undergo other carbonyl addition reactions readily.

5.2 Reactions of 3-[[(*p*-Nitrophenyl)Sulfonyl]Oxy 2-Keto Esters

Reductions of the carbonyl group, although often considered as a separate type of carbonyl reaction, are in fact best described as addition of hydride to the carbonyl. The most common method for reduction of ketones is the use of sodium borohydride in ethanol. The reaction of **15b** with sodium borohydride in absolute ethanol did not afford **18b** as expected. After aqueous work-up, a pale yellow solid, which polymerized into second solid that was only soluble in acetone/water solution, was obtained.

In light of the previous hydration experiments, it seems likely that carbonyl addition by ethanol may have competed with reduction of the carbonyl group (Equation 93). Ethanol may have added to the carbonyl group to give hemiketal, **70**, and intramolecular displacement of the nosylate group would afford an α -ethoxy glycidic ester, **71**. This same type of intramolecular displacement was seen previously in the reaction of α -nosyloxy ketones with methoxide (Equation 29).⁸³ Compound **71** would not be very stable and consequently could undergo ring opening. Many possible reaction pathways

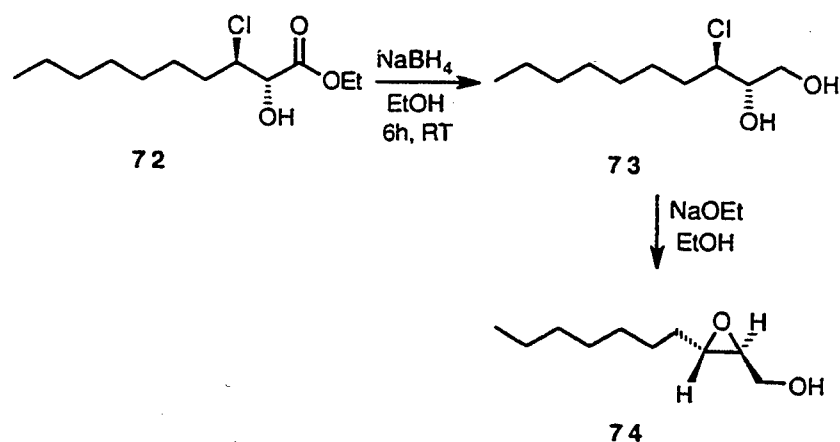
could have occurred, such as reduction and hydrolysis, but most probably, the final product was composed of a significant proportion of oligomeric alcohols.



Equation 93

Sodium borohydride is widely regarded as unsuitable for reducing simple esters under normal reaction conditions, but certain conditions such as the presence of metal salts and high temperature or large excess of sodium borohydride in methanol can give reduction of the ester group.¹⁴⁵ Recently, it has been reported that the slow addition of methanol to refluxing mixture of sodium borohydride and an ester in *t*-butanol gives alcohols in high yields.¹⁴⁶ Electrophilic, activated esters such as oxo and hydroxy esters, are easily reduced by sodium borohydride, and consequently, sodium borohydride has been described as a "nucleophilic" reducing agent¹¹⁴ since the ease of reduction is related to the electrophilicity of the carbonyl. For example, reaction of ethyl (2*S*,3*S*)-3-chloro-2-hydroxy-decanoate, **72**, and sodium

borohydride for six hours at room temperature provided (2*S*,3*R*)-3-chloro-1,2-decanediol, **73**, in 90% yield (Equation 94).⁴⁴ Intramolecular ring closure of **73** provided (2*S*,3)-2,3-epoxydecanol, **74** in 60% yield. Thus it is also possible that reduction of **15b** to afford triols could have taken place as well.



Equation 94

The reduction of **15b** with sodium borohydride possibly failed due to the competing addition of solvent to the carbonyl group and due to the over-reduction of the ester group by sodium borohydride. In any case, this experiment exemplifies a common problem of 1,2,3-trifunctionalized molecules. While attempting to reduce the ketone, the adjacent ester group can, by its proximity, be reduced in a subsequent, intramolecular reaction; therefore, the normally reliable reduction of ketones using sodium borohydride in ethanol fails in the polyfunctional environment. As it appeared that reduction of the ester carbonyl was occurring as well as the ketone, selective

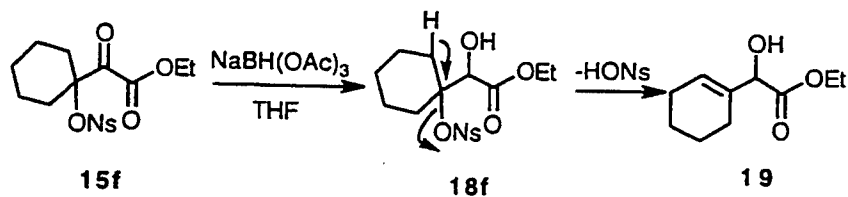
reduction of the ketone carbonyl by utilizing a milder reducing agent was investigated.

The reactivity of sodium borohydride can be tempered by the addition of methanol. It has been postulated that the methanol reacts with sodium borohydride to form methoxyborohydrides, which are more reactive as reducing agents than sodium borohydride itself (Equation 95).^{111,113} Careful addition of a slight excess of methanol produces a reactive reagent containing only about one equivalent of available hydride ($\text{NaBH}(\text{OMe})_3$). Since the reduction of the ketone group of **15b** requires only a single equivalent of hydride, it was felt that conversion of sodium borohydride to a hydride limited reagent would be beneficial.



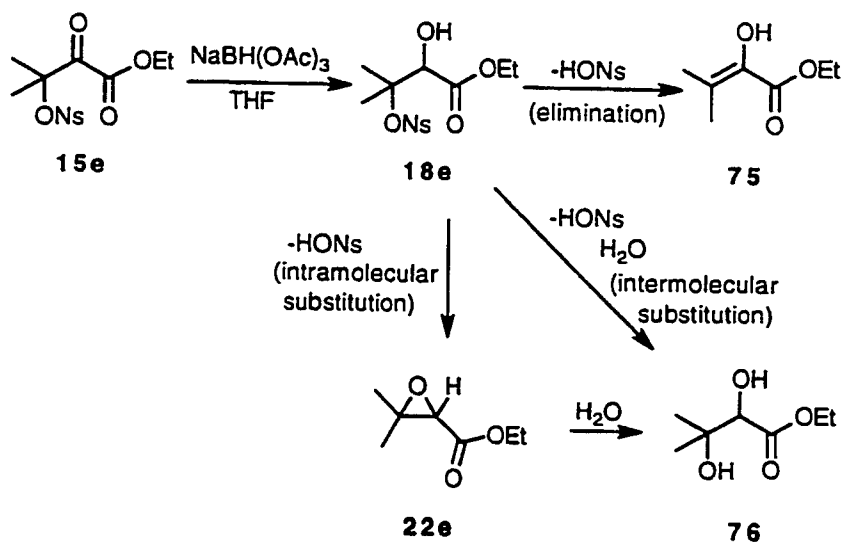
Equation 95

The amount of methanol added is important, since addition of excess methanol to sodium borohydride causes the rapid loss of more than 80% of the available hydride.¹⁴⁷ A different solvent system was required, and after examination of the literature, the mixed solvent system of THF:MeOH (99:1) was chosen.¹¹⁵ The modified reducing agent gave much improved results for the reduction of **15b** and **15c** (Equation 52), and only fair results with **15a** (Table 8). Although the results for the reductions were improved, this preparation still appeared to be too reactive for some of the more sensitive substrates. Thus, an even milder reducing agent that was suitable for a range of β -nosyloxy- α -keto esters was sought.



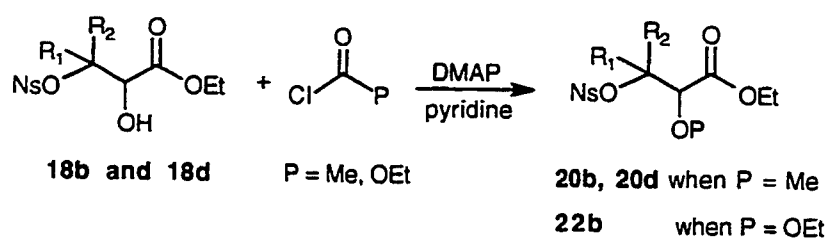
Equation 96

Reduction of **15e** gave the reduction product, **18e**, as part of a complex mixture (Equation 97). Although complete resolution of the mixture was not achieved, it was clear that subsequent reactions of **18e** involved loss of the nosyloxy group. The elimination product, alkene **75**, and the intramolecular substitution product, glycidic ester **22e**, were present. Diol **76** was also part of the product mixture, and hydrolysis of either **18e** or **22e** could have led to the formation of **76**.



Equation 97

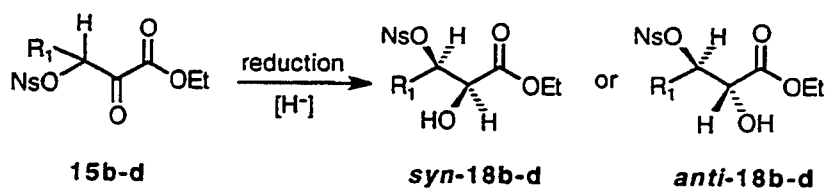
The hydroxy nosylates **18a-d** were not stable to silica gel chromatography, and since **18d** was an oil, no purification method could be found to separate the two sets of diastereomers. Protection of the reactive hydroxyl group was necessary to permit the separation by chromatography. Reaction of **18b** and **18d** with either acetyl chloride or ethyl chloroformate provided the acetate ester or carbonate ester in good to excellent yields (Equation 98). Of the two protection methods, the protection of the hydroxyl group as an acetate ester provided better yields. Fortunately, pyridine and DMAP required for the protection synthesis were not strong enough bases to cause elimination of the nosylate group, and the diastereomers of acetylated **18d** were efficiently separated by HPLC.



Equation 98

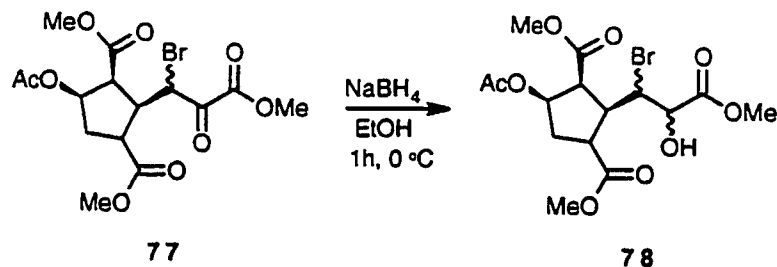
Although the reduction of **15d** with sodium triacetoxyborohydride gave an (55:45) mixture of the *syn* and *anti* diastereomers, the reductions of **15b** and **15c** with sodium borohydride and the sodium triacetoxyborohydride both gave a single diastereomer (Equation 99). The rate of reduction with sodium triacetoxyborohydride was significantly slower (overnight) than the rate of reduction with sodium borohydride (less than one hour). The triacetoxy

groups appear to retard reduction markedly, but they have little effect on the stereoselectivity of the reaction.



Equation 99

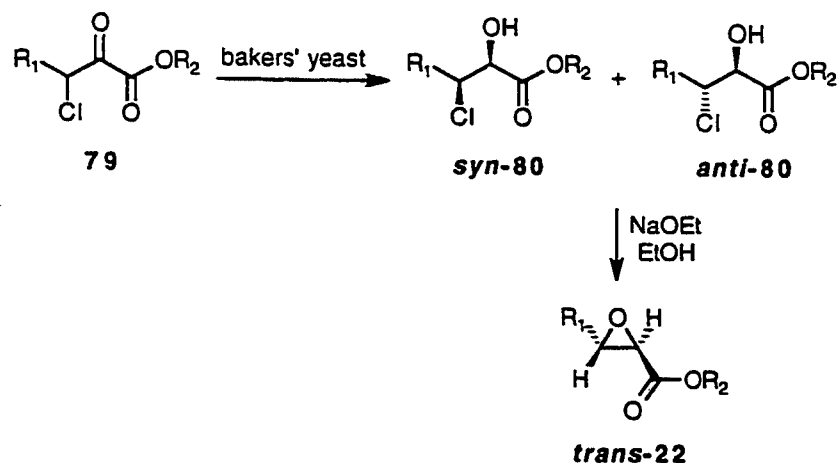
Reduction of a similar functional array, β -bromo- α -keto esters, has also been studied.⁶⁹ Although the authors did not report the *syn* to *anti* ratio, the reduction of β -bromo- α -keto ester, **77**, with sodium borohydride in ethanol at 0 °C provided the β -bromo- α -hydroxy ester, **78**, as a mixture of diastereomers (Equation 100). Clearly, the reduction of β -nosyloxy- α -keto esters (Equation 99) is more diastereoselective than the reduction of β -bromo- α -keto esters (Equation 100). This illustrates the simplified chemistry of the nosyloxy group in comparison to halogen leaving groups. Although the reduction of **15b** and **15c** was highly diastereoselective, it was not possible to assign the



Equation 100

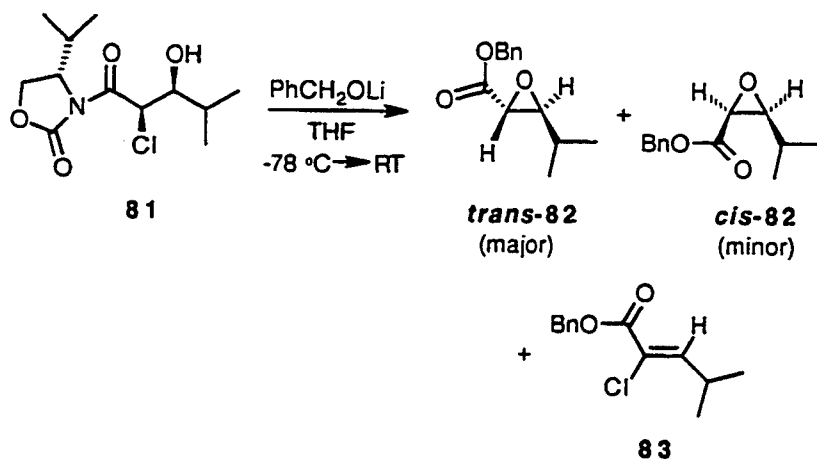
stereochemistry of the reduced product solely on the basis of coupling constants and chemical shifts. Ring closure to glycidic esters, which have distinctive chemical shifts and coupling constants, was viewed as a viable method for determination of the stereochemistry of the reductions.

Only one example of similar a β -chloro- α -hydroxy ester base-promoted ring closure has been reported.⁴⁴ The chlorohydrins were prepared by the enzymatic reduction of β -chloro- α -keto esters, **79**, to afford a mixture of the *anti*(2*S*,3*R*) and *syn*(2*S*,3*S*) β -chloro- α -hydroxy esters, **80** (Equation 101). These biological reductions provide an almost equal mixture of the *syn* and the *anti* products when two chiral centers are produced.⁴³ Treatment of the mixture of *syn* and *anti* β -hydroxy- α -chloro esters, **80**, with sodium ethoxide in ethanol provided the *anti*-glycidic esters. The ring closure for β -hydroxy- α -chloro esters is not stereoselective, and epimerization causes the *trans* glycidic ester to predominate regardless of the initial *syn* to *anti* ratio.



Equation 101

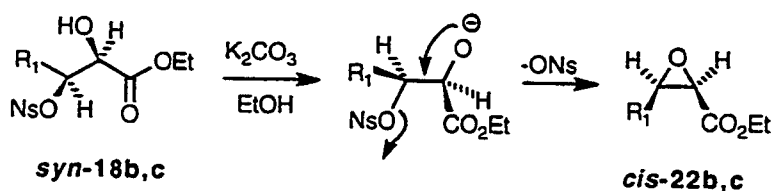
Epimerization was also observed for the ring closure of a mixture of *syn* and *anti* β -hydroxy- α -chloro esters to afford predominately *trans*-**22**.^{39,43} In fact, pure *syn*- β -hydroxy- α -chloro ester, **81**, was converted in 74% yield to a mixture of mostly the *trans* glycidic ester, *trans*-**82**, a trace of the *cis* glycidic ester, *cis*-**82**, and minor amount (4%) of the elimination product, **83** (Equation 102).³⁸ The same authors also found, however, that the bromo analog to **81**, *syn*- β -hydroxy- α -bromo ester, undergoes stereospecific base-promoted ring closure to afford only *cis*-**82** (Equation 12). Similarly, ring closure of β -hydroxy- α -tosyloxy esters with potassium carbonate in wet DMF was reported to afford stereospecific ring closure.⁵² Other workers have not been able to verify the stereospecificity of ring closure with the potassium carbonate in wet DMF method.⁹¹ Clearly, chlorohydrins, no matter the regiochemistry or the cyclization conditions, epimerize to give the *trans* glycidic esters. Ring closure using more reactive leaving groups, such as bromide and tosylate,



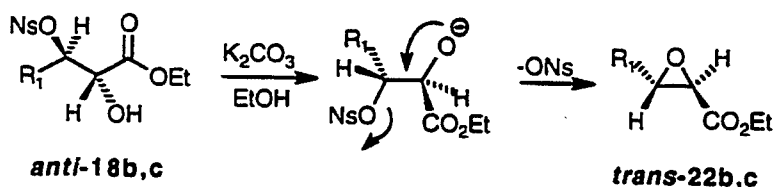
Equation 102

afford glycidic esters stereospecifically, so long as the proper conditions are utilized.

In order to assign the stereochemistry of the reduction products **18b** and **18c**, no epimerization of the starting material, **18b** and **18c**, can occur during ring closure. Sharpless found that potassium carbonate in ethanol is a superior reagent for this purpose,⁶⁷ and the stereoselectivity of the ring closure is high with these reagents. Ring closure of the *syn* or *anti* isomers of β -nosyloxy- α -hydroxy esters, **18b** and **18c**, was expected to occur without loss of stereochemical integrity. Consequently, *syn*-**18b** and *syn*-**18c** β -nosyloxy- α -hydroxy esters give *cis* glycidic esters, *cis*-**22b** and *cis*-**22c**



(Equation 103), and *anti*-**18b** and *anti*-**18c** β -nosyloxy- α -hydroxy esters afford *trans* glycidic esters, *trans*-**22b** and *trans*-**22c** (Equation 104).



Reported chemical shifts^{38-40,43,44} for the C₂ proton of *cis* glycidic esters are 3.4-3.7 δ and chemical shifts for the C₂ proton of *trans* glycidic esters are 3.2-3.5 δ . Typical coupling constants for the C₂ and C₃ protons of *cis* glycidic esters are around 4.6 Hz, and coupling constants for the *trans* glycidic esters are around 1.8 Hz. When **18b** and **18c** were converted to glycidic esters **22b** and **22c** by potassium carbonate in ethanol, the ¹H NMR spectra indicate that they are both the *cis* isomers. Consequently, **18b** and **18c** were both the *syn* diastereomers; thus, reduction of **15b** and **15c** is *syn* diastereoselective. No epimerization was observed with the reagents employed.

Although, other general methods for the preparation of glycidic esters, such as the Darzen's synthesis³⁶⁻³⁸ and use of the Sharpless asymmetric epoxidation,⁴⁹⁻⁵¹ are well developed and are efficient synthetic routes to these compounds, the ring closure of **18b** and **18c** to glycidic esters offers a special diversity of synthetic strategy. The pK_a of the C₂ O-H proton of the β -nosyloxy- α -hydroxy esters is estimated to be about 11-12.⁶⁷ Therefore, if the ring closure reaction was required in a synthetic strategy, the ring closure could be achieved stereoselectively even in the presence of other hydroxy groups in the molecule. Also, prior protection of the other hydroxyl groups would be unnecessary due to the enhanced reactivity of the C₂ hydroxy group.

One model used for the explanation of the stereochemical course of 1,2-asymmetric addition reactions of ketones with metal hydride reagents is Cram's model (Figure 14).¹⁴⁸ In this model, the nucleophile approaches the eclipsed conformation of the carbonyl compound from the least hindered side



unfavored

of the carbonyl group. Applied to the borohydride reduction of β -nosyloxy- α -keto esters **15b** and **15c**, this model predicts that the *anti*-diastereomer should be favored (Equation 105). In fact, the *syn*-diastereomer is the major product; therefore, Cram's model is inconsistent with the observed results and doesn't predict the proper stereochemistry.



anti-18b

Another model used to explain the stereochemical course of addition to ketones is the Felkin-Anh model.^{149,150} This model assumes that the transition state is reactant-like, and that the more important transition state interactions occur between the entering group and the achiral group attached to the carbonyl group. The premises of the Felkin-Anh model lead to a

transition state where the entering group approaches antiperiplanar to one of the substituents bound to the asymmetric center.¹⁵¹

For the reductions of **15b** and **15c**, there are four possible conformers **A**, **B**, **C**, **D** in which either the nosylate group or the R group is antiperiplanar to the carbonyl π -system (Figure 15). The R group is antiperiplanar to the carbonyl π -system in conformers **A** and **B**, and in conformations **C** and **D**, the nosylate group is antiperiplanar to the carbonyl π -system. Of these four, conformers **B** and **D** can be removed from consideration because steric

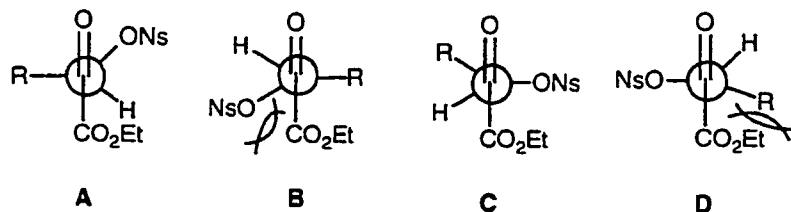


Figure 15. Possible Felkin-Anh Conformers for Reduction of **15b,c**

repulsions between the nosylate group and the ester group in conformer **B** and between the benzyl group and the ester group in conformer **D** raises the relative energies of conformers **B** and **D** relative to conformers **A** and **C**. This leaves conformers **A** and **C** as the most likely reactive conformers (Figure 16). Addition of hydride to conformer **A** leads to the *anti*-**18**, and addition to conformer **C** leads to *syn*-**18**.

Two opposing effects, steric and electronic effect, determine the conformational preferences. While the benzyl group, R, is sterically larger than the nosylate group, conformer **C** is favored because in the Felkin-Anh model, "largeness" is dictated by the polarity of the bond to a group in the α -

position. The more polar is the bond to an α -substituent, the "larger" is that group and the more it will prefer to be antiperiplanar to the carbonyl π -system.

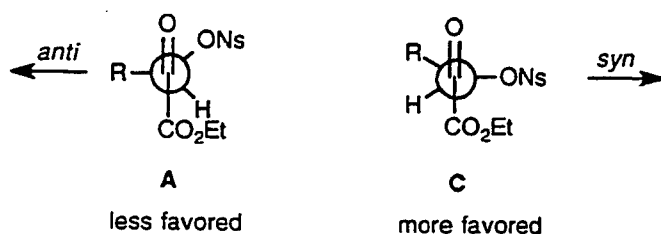
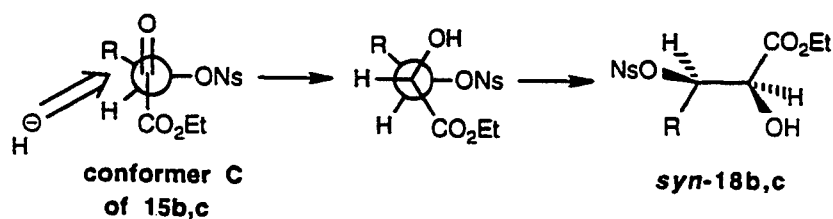


Figure 16. Favorable Felkin-Anh Conformers for Reduction of **15b-d**

Therefore, the Felkin-Anh model predicts that conformer **C** is the reactive conformer and that reduction should occur preferentially to give the *syn* isomer (Equation 106). This is in accord with the experimental results. Previous results from this laboratory⁹¹ showed that sodium borohydride reductions of β -oxo- α -nosyloxy esters had a similar *syn*-preference for a similar transition state model (Equation 36). Reductions of the β -nosyloxy- α -keto esters reported here are more selective and give only the *syn* diastereomer, whereas β -oxo- α -nosyloxy esters are *syn* diastereoselective only to the extent of 3:1.



Equation 106

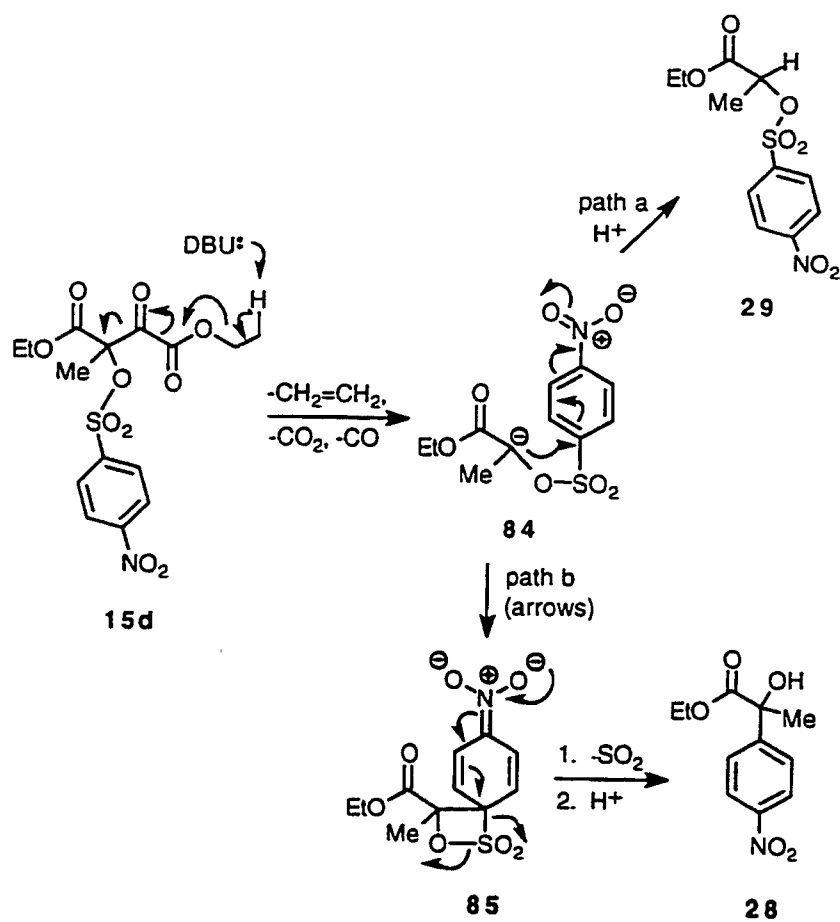
The reduction reactions of **15a-g** illustrate that the β -nosyloxy- α -keto ester functional array has an enhanced reactivity. The high reactivity of the β -nosyloxy- α -keto ester functional array was somewhat discouraging, since the "normal" reducing agents were too reactive. On the other hand, it was possible that the enhanced reactivity of β -nosyloxy- α -keto esters might provide novel routes to 1,2,3-trifunctionalized compounds not otherwise accessible from precursors of lesser reactivity. The ester group and the nosyloxy group that flank the ketone function make it extremely electrophilic and consequently very reactive. If the nosyloxy leaving group could first be replaced by a less electron-withdrawing substituent, the reactivity of the ketone might be modulated. With this in mind, a series of amine nucleophiles, including benzylamine, pyrrolidine, and morpholine, were reacted with **15b** (Equation 107). Only morpholine gave substitution for the nosyloxy group and not base-promoted chemistry, probably due to the fact that it is also the weakest base of these three nucleophiles ($pK_a = 8.4$).

Benzyl amine ($pK_a = 9.33$) and pyrrolidine ($pK_a = 11.27$) are stronger bases and base-promoted chemistry is predominant. For example, base-promoted decomposition of **15b** occurs with basic nucleophiles whose pK_a values are greater than 8.5. Therefore, nucleophiles with pK_a less than 8.5 would be the best candidates for nosylate substitution reactions. Synthetically, this means that because there are very few amines with pK_a values less than 8.5, nucleophilic substitution of **15** by amines is of limited applicability. In general, amine nucleophiles cannot be considered as viable nucleophiles for substitution reactions of β -nosyloxy- α -keto esters.



134

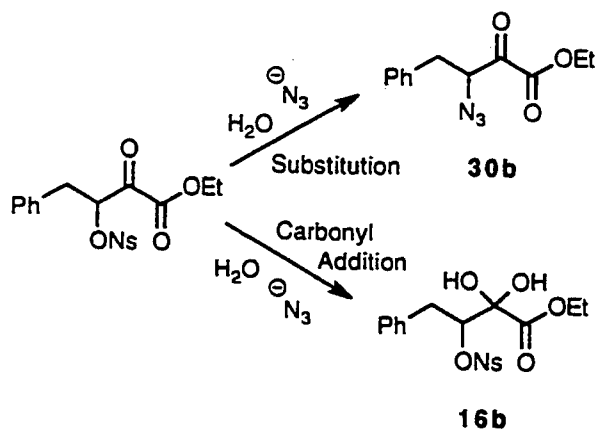
affords ethyl 2-hydroxy-2-(*p*-nitrophenyl)-propanoate, **28**. The latter pathway involving *ipso* substitution of was previously observed in the reaction of α -nosyloxy ketone enolates (Equation 31).⁸³



Equation 108

Treatment of β -nosyloxy- α -keto esters with basic amine nucleophiles caused base-promoted decomposition instead of substitution. Evidently, the ester group and nosyloxy group that flank the ketone render the ketone extremely electrophilic. Consequently, it was decided to survey a variety of processes with one β -nosyloxy- α -keto ester in order to define the types of reactions that offer the greatest synthetic potentials. Since a significant fraction of the molecular weight of a β -nosyloxy- α -keto ester is due to the nosylate group, a larger β -nosyloxy- α -keto ester was chosen as the model compound so that the reaction products would have a moderately large molecular weight after the nosylate group was lost. β -Nosyloxy- α -keto ester, **15b**, was chosen as a typical example of the group.

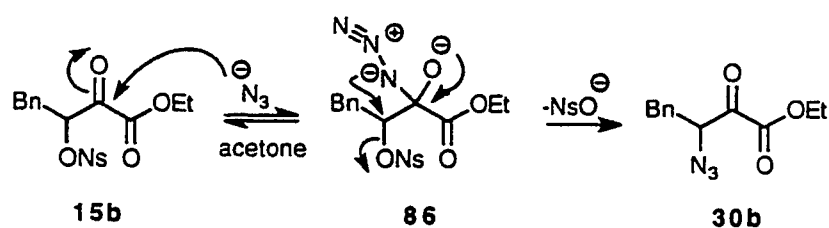
Since basic amine nucleophiles are not suitable in displacement reactions of **15b**, the azide ion (pK_a 4.75) was chosen as an attractive non-basic amine-equivalent nucleophile. Reaction of **15b** with sodium azide in wet acetone produced only the gem diol, **16b** (Equation 109). No product



Equation 109

was found that would indicate that azide ion addition to the carbonyl carbon or substitution of the nosylate group had occurred.

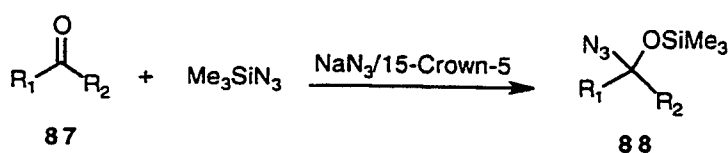
Azide ion is a better nucleophile than water, and in the absence of water, azide ion displaces the nosylate group at room temperatures in a few hours (Equation 110). Clearly, azide ion (nucleophilic constant, $n = 5.78$)¹⁵² is much more nucleophilic than the water (nucleophilic constant, $n < 0$),¹⁵² but the nosylate substitution reaction with azide ion is slower than carbonyl addition by water. Furthermore, substitution in the diol, **16b**, is much slower than in ketone, **15b**.



Equation 110

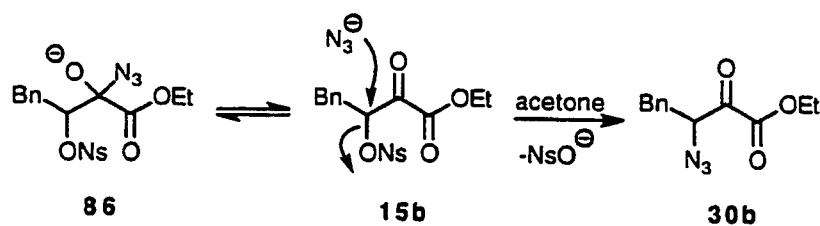
Azide ion could undergo reaction with **15b** by two modes of attack. Similar to the mechanism reported for the reaction of amines with α -nosyloxy ketones (Equation 30),⁸³ azide ion attack of the carbonyl group of **15b** would give a tetrahedral intermediate, **86**, and intramolecular displacement of the nosylate group by the azide nitrogen would provide **30b**. Other examples of carbonyl addition by azide ion are known. Trimethylsilyl azide in the presence of catalytic sodium azide and 15-crown-5 has been shown to add to carbonyls, **87**, to give siloxy azides, **88**, (Equation 111).¹⁵³ When excess

trimethylsilyl azide in the presence of zinc chloride or tin(II) chloride was used, *gem*-diazides were produced.¹⁵⁴



Equation 111

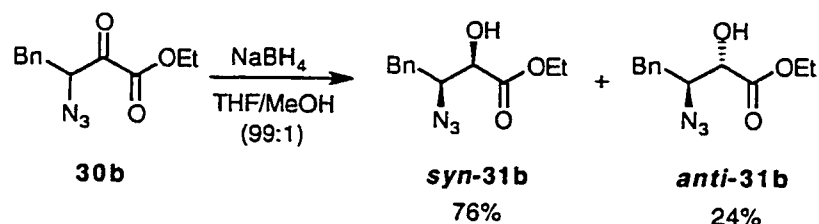
However, no evidence for the formation of **86** in the ¹H and ¹³C NMR data was found. A more likely mechanistic scenario involves direct nucleophilic displacement of the nosylate group by the azide ion (Equation 112). Patonay⁸⁴ found that reaction of α-nosyloxy ketones with sodium azide apparently proceeds by direct displacement of the nosylate group by a S_N2 process. The same type of mechanism is believed to occur in the nucleophilic attack by azide ion on α-halo ketones.¹⁵⁵ Using sodium azide in dry acetone avoided the problems of ketone hydration and azide **31b** could be formed in acceptable yields.



Equation 112

The ¹H NMR experiments showed that the β-azido-α-keto ester, **30b**, was not extremely stable, since it showed signs of decomposition after 11

hours. In spite of its instability, **30b** could be successfully used as a synthetic intermediate. Reduction of **30b** worked well to afford β -azido- α -hydroxy ester, **31b**, as a mixture of *syn:anti* diastereomers in a ratio of 76%:24% (Equation 65). The *syn* and *anti* assignments were deduced from published spectral data and coupling constants for *anti*-**31b** and other derivatives of **31**.⁴⁹



Equation 65

The azide group does not provide as much selectivity in the reduction of the carbonyl group as the nosylate group did, since a mixture of the *syn* and the *anti* diastereomers was obtained for the reduction of **30b**. As with the reductions of **15b** and **15c**, the Felkin-Anh model may be used to explain the observed stereoselectivity.^{149,150} There are four possible conformers **E**, **F**, **G**, **H** (Figure 17). Conformer **E** and **F** have the R group antiperiplanar to the carbonyl group, and in conformer **G** and **H**, the nosylate group is

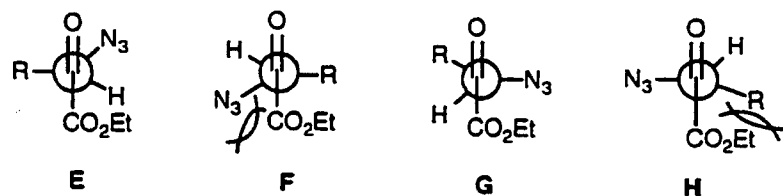


Figure 17. Possible Felkin-Anh Conformers for Reduction of 30b

antiperiplanar to the carbonyl group. Conformers **F** and **H** can be removed from consideration due to steric repulsion between the azide group in conformer **F** and the benzyl group in conformer **H** with the ester group.

Conformers **E** and **G** are the favored conformers for the reduction of **30b** with sodium borohydride (Figure 18). Addition of hydride to conformer **E**

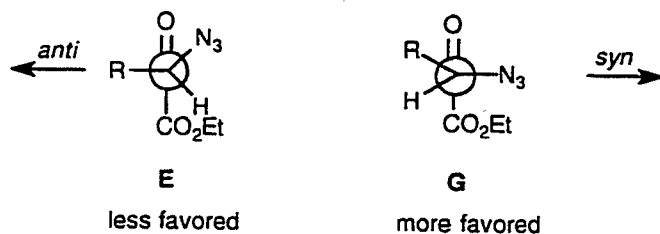
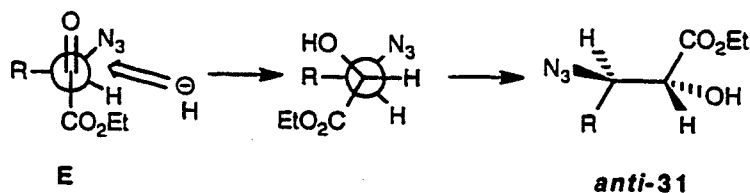


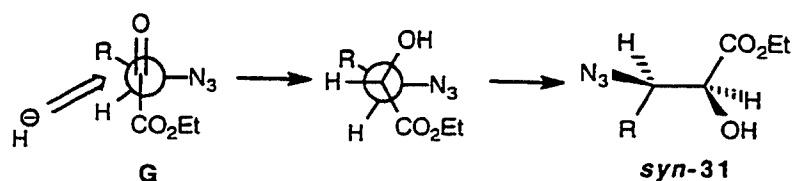
Figure 18. Favorable Felkin-Anh Conformers for Reduction of **30b**

provides **anti-31b** (Equation 113) while addition to conformer **G** leads to **syn-31b** (Equation 114). As before, the determination of the most favored conformer depends upon the balance between opposing steric and electronic effects. The *A* value for the azide group is assumed to be similar to the halogens (0.45)¹⁵⁶ but less than that for the nosylate group (0.52).⁹¹



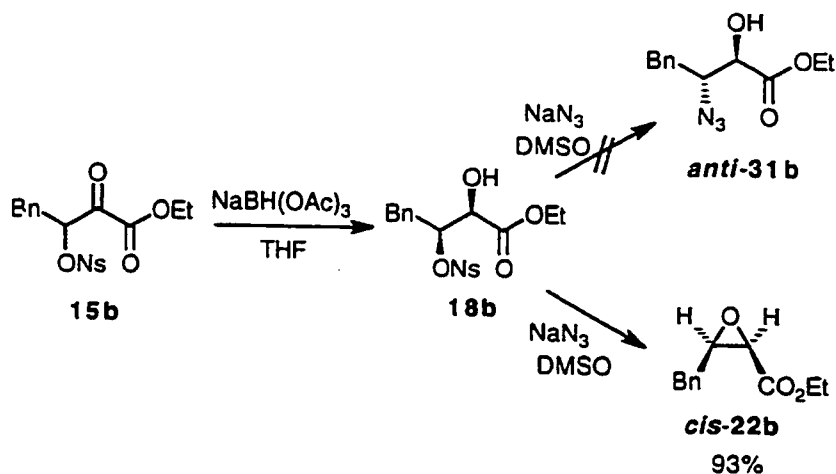
Equation 113

Therefore, the steric requirement of an azide substituent is less than that for the nosylate group. More importantly, the azide group is less electron withdrawing than the nosylate group, so that conformers **G** and **E** are closer in energy leading to reduced stereoselection compared to the reduction of nosylate **15b** (Equation 106).



Equation 114

An alternate route to azido alcohol **31b** by ketone reduction followed by nosylate displacement was examined (Figure 8). As discussed previously,

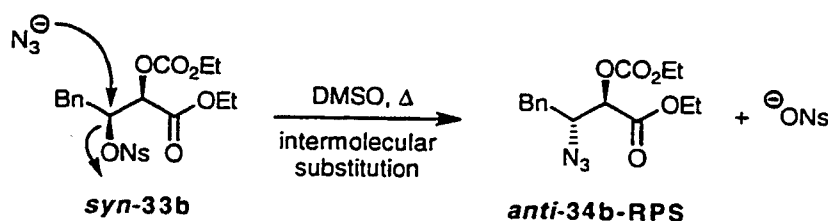


Equation 67

reduction of **15b** by sodium triacetoxyborohydride gave **syn-18b** (Equation 103). Treatment of **syn-18b** with sodium azide gave ring closure to the glycidic ester, **cis-22b**, rather than nucleophilic displacement (Equation 67). The ring closure of **18b** with sodium azide may not be too surprising when the acidity of the α -hydroxyl proton is considered. A typical hydroxyl proton has a pK_a of 15-16. A neighboring carbonyl group causes the pK_a of the OH group to drop to 11-12.⁶⁷ In fact, it was recently shown that *threo*-2,3-dihydroxy esters could be selectively sulfonylated at the α -OH by taking advantage of the acidity difference between the two hydroxyl groups.^{52, 67} The acidity of the α -OH group allows bases as weak as azide ion to promote ring closure. In order to avoid azide induced ring closure, protection of the hydroxyl group of **18b** with ethyl chloroformate gave **syn-33b**, ethyl 3-[(*p*-nitrobenzenesulfonyl)]oxy]-2-carboethoxy-4-phenylbutanoate (Equation 68).

With the protected β -nosyloxy ester **33b** in hand, the azide substitution reaction was investigated. Reaction of **33b** with sodium azide in dry acetone failed to give a substitution product and returned only starting material. The solvent was changed to DMSO, and the reaction was repeated at 60 °C (Equation 70). Three products were obtained. Direct displacement of the nosyloxy group by the azide ion produced **anti-34b-RPS** with inversion of the stereochemistry at C_3 (Equation 115). Since inversion of the stereochemistry at C_3 occurs, the bimolecular nucleophilic substitution could be viewed as a normal S_N2 type of reaction. Two elimination products ethyl 2-carboethoxy-3-ene-4-phenyl butyrate, **35**, and ethyl 2-carboethoxy-2-ene-4-phenyl butyrate, **36**, were obtained as well. Therefore, the simple S_N2 reaction of azide with

the nosylate group of **33b** affords **34b**, and simple elimination of nosic acid provides the elimination products **35** and **36**.

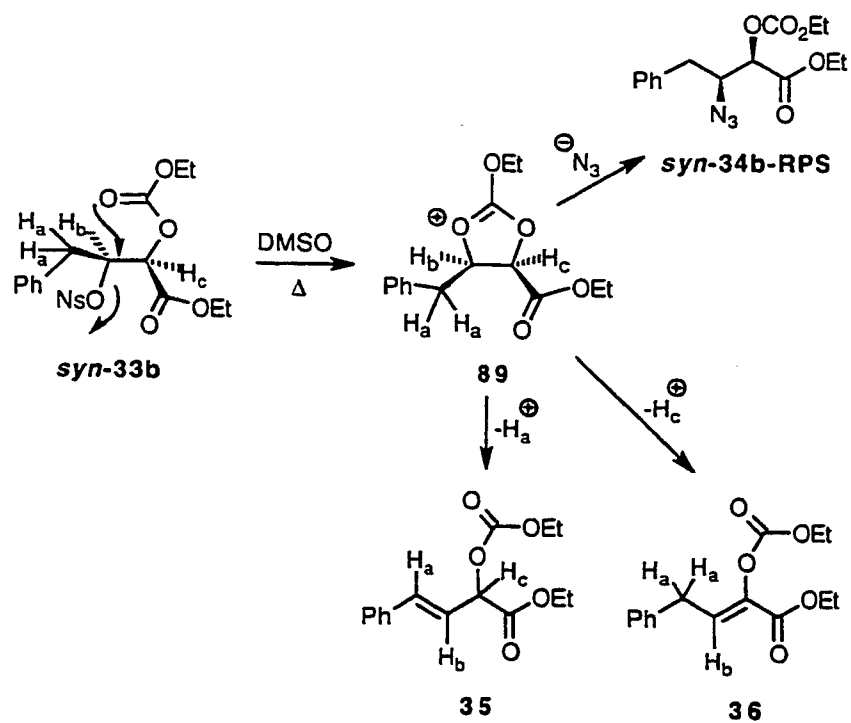


Equation 115

Another possible mechanistic scenario includes the intramolecular displacement of the nosylate group by the oxygen of the carboethoxy group to give intermediate **89** (Equation 116). Loss of an H_a proton affords **35**, where the newly formed double bond is conjugated with the phenyl ring. Likewise, loss of H_c proton would produce **36** where the double bond is conjugated with the ester group. If azide ion attacked **89**, then the *syn*-**34b** would be obtained, resulting from two successive inversions at C_3 . Therefore, *anti*-**34b** must result from a single inversion of configuration and could not originate from **89**. *Anti*-**34b** must result from direct displacement of nosylate in *syn*-**33b** or by its prior epimerization.

More stringent reaction conditions (DMSO, 60 °C) were required to successfully achieve substitution in the protected nosyloxy ester **33b** than were required to produce the same type of substitution reaction in β -nosyloxy- α -keto ester, **15b** (acetone, RT). This is due to the electron withdrawing carbonyl group at C_2 of **15b**, which makes C_3 more electrophilic. Also, the

carbonyl group is sterically smaller than a tetrahedral carbon, thus reducing steric crowding in the S_N2 transition state of **15b**.



Equation 116

These experiments were undertaken with the hope of using β -nosyloxy- α -keto esters, **15**, as precursors to 3-azido-2-hydroxy esters and ultimately 3-amino-2-hydroxy esters. Two different sequences of ketone reduction and nosylate substitution were investigated and are summarized (Figure 19). Starting from β -nosyloxy- α -keto ester **15b**, the sequence of azide

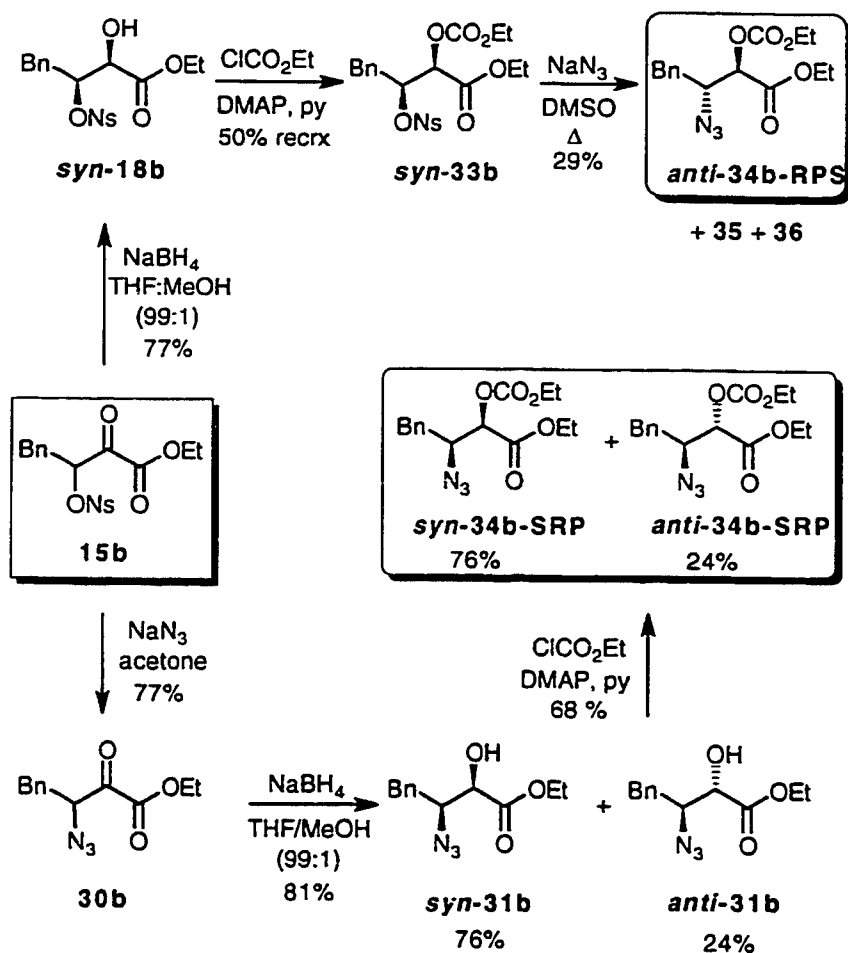


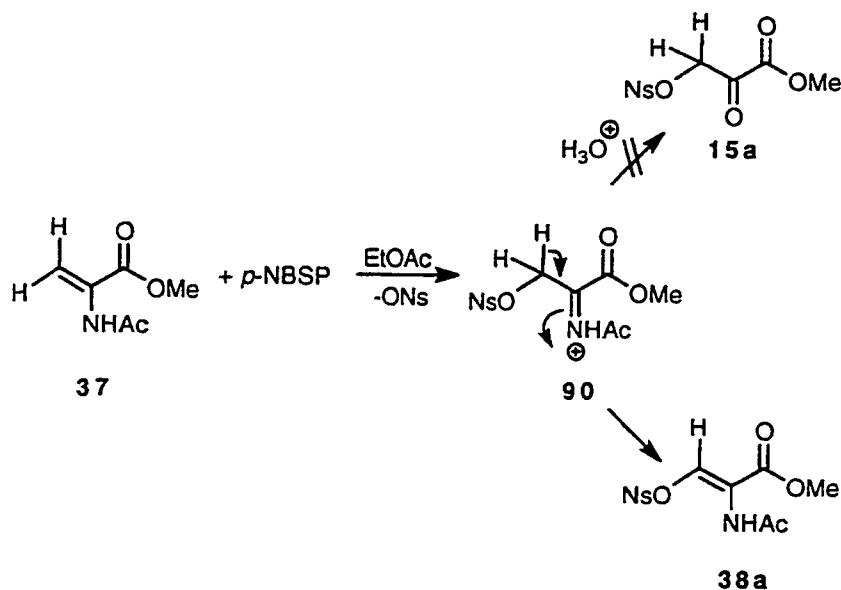
Figure 19. Summary of Azide Substitution and Reduction Sequences

substitution followed by ketone reduction and protection gives a good overall yield but only a 3:1 diastereoselectivity in the reduction step (Figure 19, lower

pathway). In contrast, the sequence of ketone reduction and protection followed by azide substitution (Figure 19, upper pathway) was highly diastereoselective but gave only modest yields of *anti*-**33b** due to competing elimination reactions in the azide substitution step. Thus, while both sequences did provide the product being sought, each had drawbacks and the reduction-protection-substitution method (Figure 19, upper pathway) required a hydroxyl protection which we had hoped to avoid. Consequently, a different approach to 1,2,3-trifunctional products from **15b** was pursued.

A major difficulty with the procedures studied this far was that the reaction conditions were basic, and it became abundantly clear that β -nosyloxy- α -keto esters **15** were quite base sensitive. For these reasons, it was thought that neutral or acid-catalyzed reactions might be a better choice for transformations of **15b**. Support for this approach came from unexpected results of an early procedure (Equation 72) for the preparation of **15** from the reaction of *N*-acyl enamides, **37**, with *p*NBSP. It had been anticipated that the enamides would react as an electron rich double bond with *p*NBSP similar to the other enol ether derivatives.⁷⁶ Instead of **15a**, the reaction gave only vinyl nosylate, **38**, in low yields (Equation 117). Evidently, intermediate, **90**, loses a proton to give **38** before hydrolysis occurs. Because of the low yields, no further work on the reaction was carried out. However, the unusual polyfunctional array in **38** make it an interesting synthetic target, thus other routes to **38** were considered.

Condensation reactions of **15b** with amides and carbamates were postulated as a possible route to compounds like **38**. Reaction of **15b** with methyl carbamate in refluxing toluene gave two products (Equation 73). The

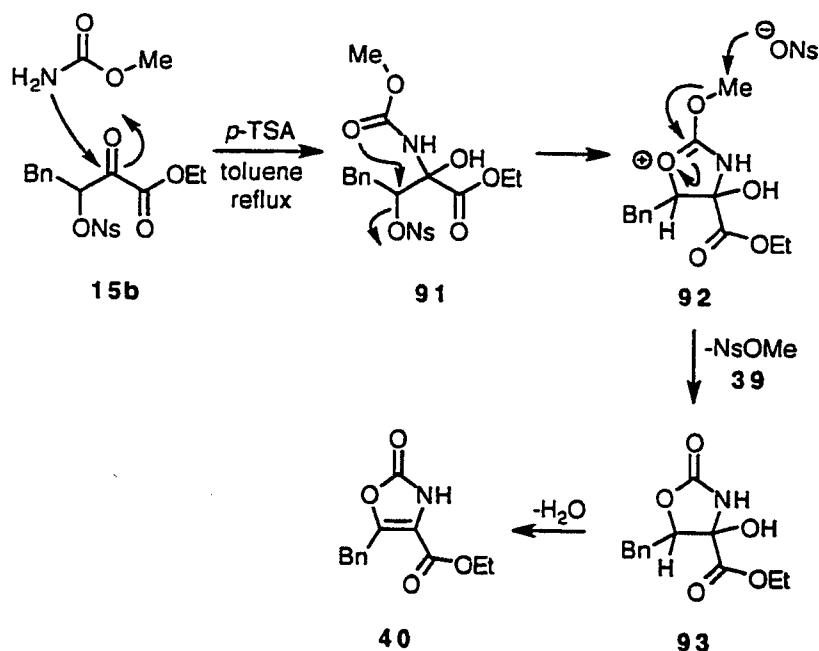


Equation 117

first product was methyl 4-nitrobenzene sulfonate, **39**, and the second compound was found to be 4-carboethoxy-5-benzyl-2-[3*H*] oxazolone, **40**, or its regioisomer, 4-benzyl-5-carboethoxy-2-[3*H*] oxazolone, **41**. The spectral data obtained for the oxazolone were not sufficient to distinguish between the two possible regioisomers, but structure **40** was favored based on the similarity of **40** to the oxazole structure **42**.

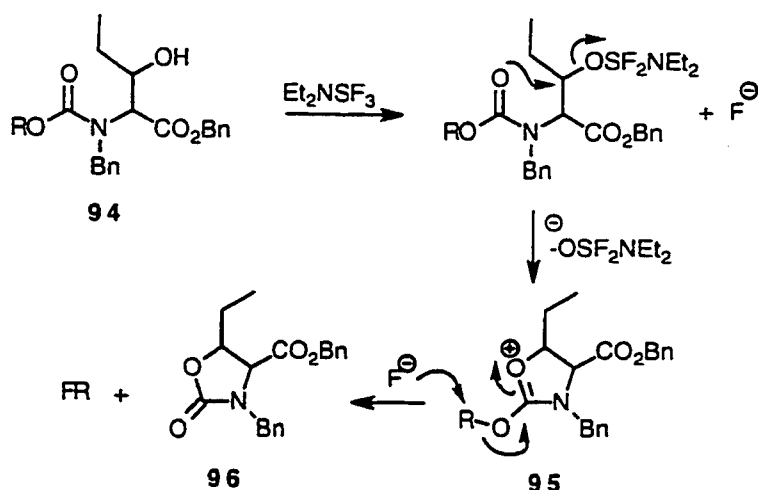
A plausible mechanism for the reaction of **15b** with methyl carbamate, begins with the carbamate nitrogen attacking the ketone carbonyl group of **15b** to afford carbinolamide intermediate **91**. Intramolecular attack by the carbamate carbonyl group on the nosylate group provides the cyclized intermediate, **92**. Demethylation of **92** by the nosylate anion would give

methyl 4-nitrobenzene sulfonate, **39**, and **93**. Subsequent loss of water from **93** provides **40**. Although it is not shown (Equation 118), an unproductive initial equilibrium involving addition of the carbamate oxygen instead of the carbamate nitrogen to the ketone group of **15b** could also occur. Initial attack by the carbamate nitrogen to afford product is quite reasonable. The condensation of amides and carbamates with ketones by nitrogen addition to the carbonyl group results in *N*-alkylated products, as was also seen for the condensation of amides and carbamates with pyruvate esters (Equation 71).



Equation 118

Once the tetrahedral intermediate **91** is formed, cyclization and demethylation follow. Although nosylate ion is not a good nucleophile, a similar mechanism for another poor nucleophile, fluoride ion, has been reported for the cyclization of β -hydroxy- α -amino acid ester, **94**, upon treatment with (diethylamino)sulfur trifluoride, DAST (Equation 119).¹⁵⁷ Sulfonylation of **94** followed by intramolecular displacement by the carbamate oxygen affords intermediate **95**. Demethylation of **95** by fluoride yields oxazolidinone, **96**. This sequence is essentially the same as the mechanism proposed (Equation 118) and shows that even poor nucleophiles such as fluoride or nosylate are capable of demethylating oxonium ion intermediates.



Equation 119

The product obtained by the reaction of **15b** with methyl carbamate is an oxazolone, in particular a 4-oxazolin-2-one or a 2 (3H)-oxazolone, where

the numbering of the ring begins at the oxygen and works clockwise around the ring (Figure 20).¹⁵⁸ There are no examples of oxazolones in the literature in which either R₂ or R₃ is a carboxylic acid derivative.¹⁵⁸ The most

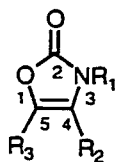
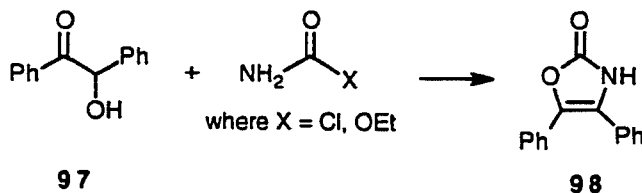


Figure 20. General Structure for 4-oxazolin-2-one

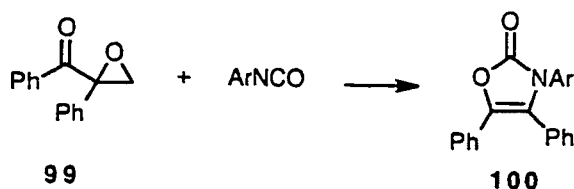
common synthetic route to 4-oxazolin-2-ones uses the condensation reaction of α -hydroxy ketones, most often benzoin **97**, with ethyl carbamate or ethyl chloroformate to give 4,5-diphenyl-4-oxazoline-2-one, **98** (Equation 120).¹⁵⁸ Two variations of this reaction include the reactions of α -bromocarbonyl compounds with potassium isocyanate,¹⁵⁸ and the reaction of α -hydroxy ketones with dichloroformate and ammonia to afford the oxazolones.¹⁵⁸



Equation 120

Other routes to 4-oxazolin-2-ones include reactions of 2-benzoyl-2-phenyloxirane, **99**, with aryl isocyanates to afford aryl substituted oxazolones, **100** (Equation 121).¹⁵⁸ In general, preparations of the 4-oxazolin-2-one class

of oxazolones are not well known. The condensation of β -nosyloxy- α -keto esters, **15**, with carbamates appears to provide a much simpler and higher yielding route to 4-oxazolin-2-ones. Before the full potential of the reaction of **15** with carbamates can be realized, the mechanistic details of the reaction must be confirmed, but the literature does not provide precedents for this process. Therefore, in order to understand more about the synthetic utility of the reaction of **15b** with carbamates, the preparation of another well-known heterocycle, an oxazole, was examined.



Equation 121

Oxazoles are well known compounds and have been more thoroughly studied than 4-oxazolin-2-ones.^{159,160} Like oxazolones, oxazoles are also five membered heterocycles with an oxygen and a nitrogen atom in the ring (Figure 21). Oxazoles have been synthesized by a variety of methods,^{159,160} and one especially common synthesis, due to the ready availability of the

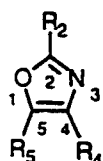
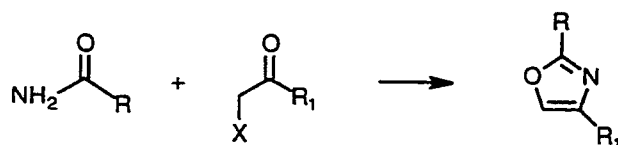


Figure 21. General Structure for 1,3-oxazole

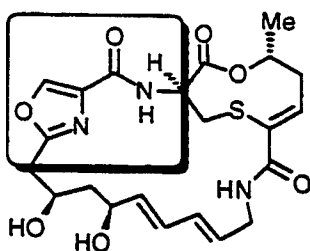
starting materials, involves the condensation of α -halo ketones, **102**, with amides, **103** (Equation 122). The reaction works well for most systems, although the condensation of α -chloroketones with amides was found to not yield oxazoles¹⁶¹ and yields of 2,4-disubstituted oxazoles tend to vary.



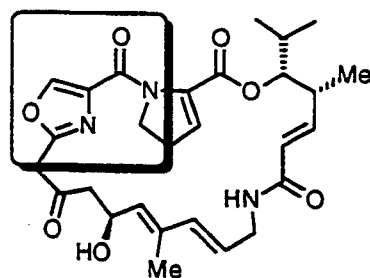
101

Equation 122

The synthesis of oxazole esters, more specifically, oxazole 4-carboxylic esters, is much more difficult. These oxazoles have recently received interest due to their presence in many natural products.¹⁶² For example, antibiotics beminamycin A,¹⁶³ griseoviridin, **102**,¹⁶⁴ virginiamycin, **103**,¹⁶⁴ and madumycin, **104**.¹⁶⁴ all contain this unique structural feature. The

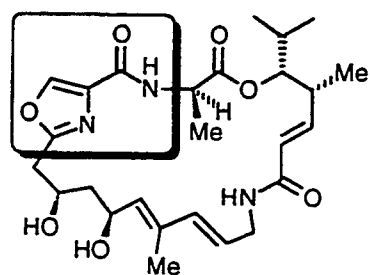


102
Griseoviridin



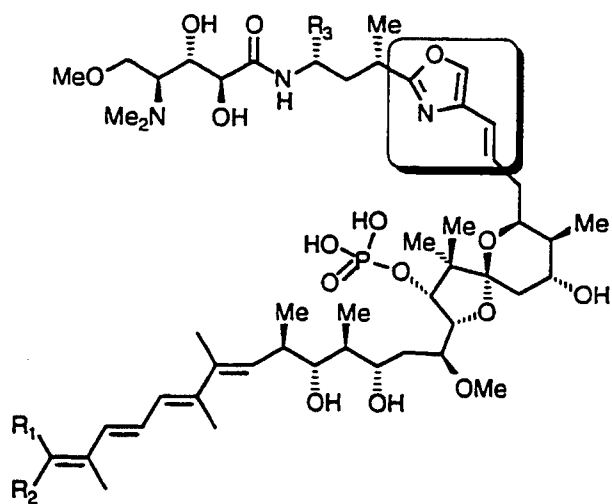
103
Virginiamycin M

synthesis of antitumor agent and phosphatase inhibitor, calyculin A, **105**,^{63,130,165,166} utilizes the 4-carboethoxy group of the oxazole as a functional handle to append the rigid alkene subunit.



104

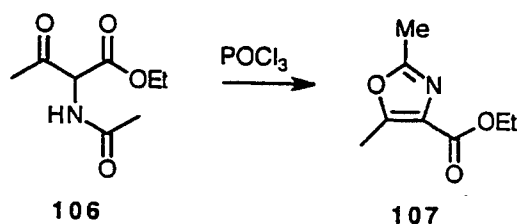
Madumycin II



105

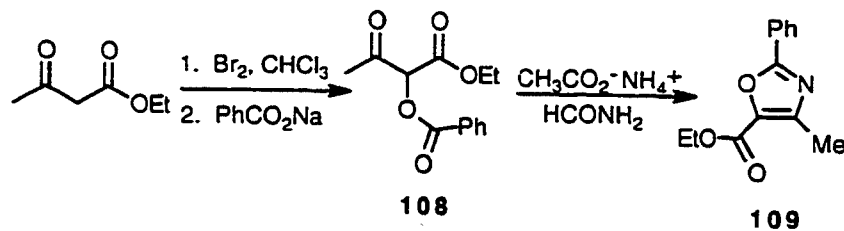
Calyculin

A common reaction sequence for the preparation of 4-carboethoxy oxazoles^{135,167} involves the intramolecular cyclization of β -keto- α -N-acetamido esters, **106**, to give the 4-carboethoxy oxazoles, **107**, in 40-93 % yield (Equation 123). The regioisomer of **107**, 5-carboethoxy oxazole, **110**,



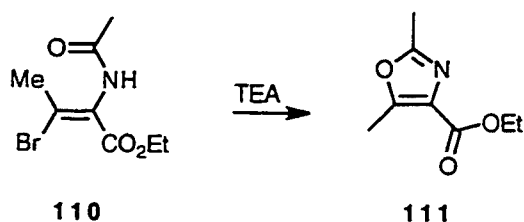
Equation 123

can be prepared (Equation 124) by α -bromination of ethyl acetoacetate to give the β -keto α -bromo ester, and treatment of the β -keto α -bromo ester with the sodium salt of benzoic acid gives the β -keto α -O protected ester, **108**, which is condensed with ammonium acetate to give 5-substituted oxazole ester, **109**.



Equation 124

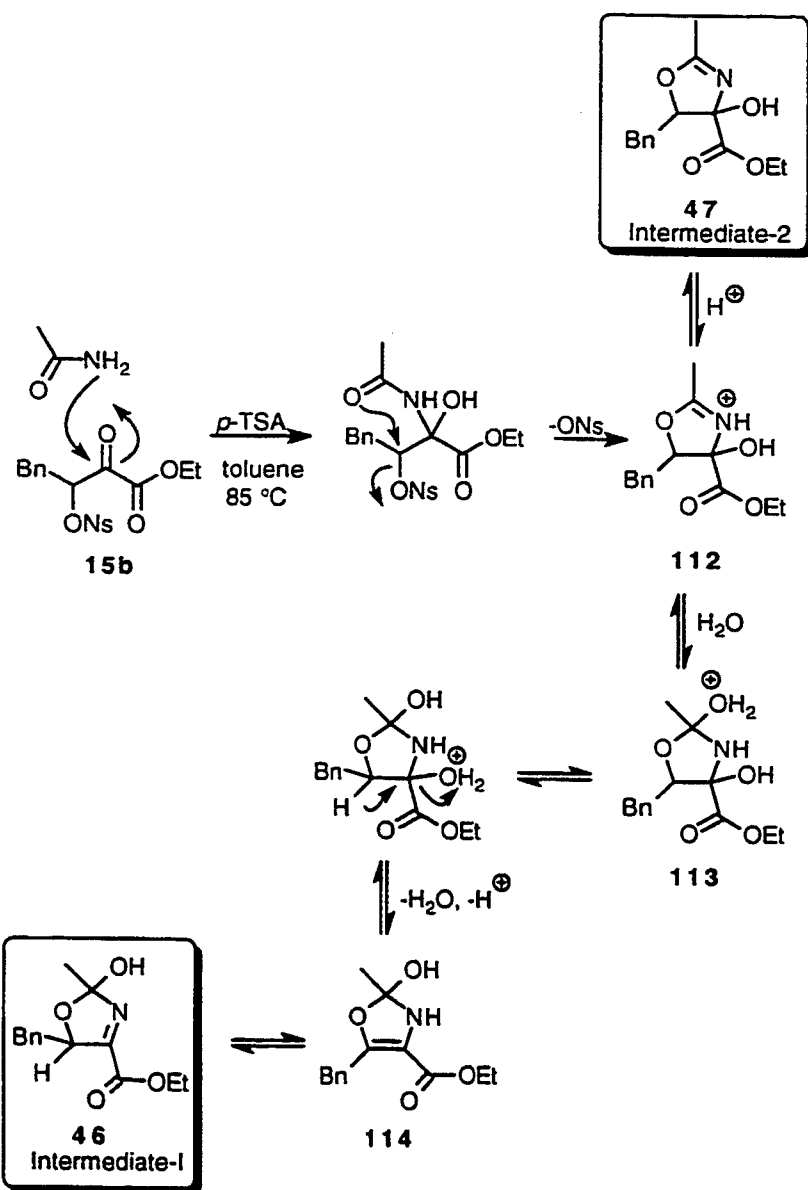
In another synthesis of 4-carboethoxy oxazoles, **111**, 2-acylamino-3-haloacrylic esters, **110**, are treated with triethylamine (Equation 125).¹⁶⁷ A simple nickel peroxide oxidation of oxazoline also can be used for the preparation of 4-carboethoxy oxazoles.^{63,168-170}



Equation 125

The reaction of **15b** and acetamide also provides 4-carboethoxy oxazoles in good yields (Equation 74). The mechanism for this reaction (Equation 126) is believed to be similar to the reaction of **15b** with the methyl carbamate. Initial attack by the amide nitrogen on the carbonyl group of **15b** and subsequent amide oxygen displacement of the nosylate group leads to a **112**. There are two pathways leading to two different intermediates from **112**. Attack by water at C₂ of **112** provides **113**, and **113** loses water from C₄ to give **114**. Tautomerization of **114** affords **46**, intermediate I. On the other hand, loss of a proton from **112** affords the second intermediate, **47**. Intermediates **46** and **47** were isolated and the structures for these two intermediates was tentatively assigned. Dehydration of **46** or **47** gives the oxazole product, **42**.

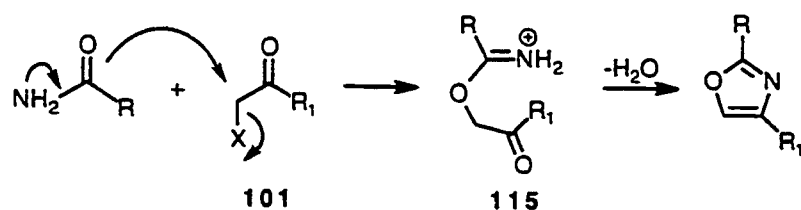
Besides the isolation of intermediates **46** and **47**, the pathway shown in Equation 126 is favored for two additional reasons. First, the ketone carbonyl



Equation 126

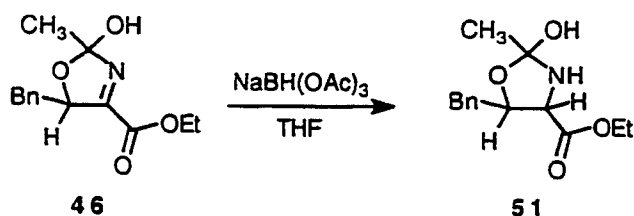
group of **15b** is extremely electrophilic, so nucleophilic addition will occur here first. Secondly, no spectral evidence of an imidate intermediate was obtained. Consequently initial addition to the carbonyl group of **15b** by the amide nitrogen followed by intramolecular cyclization seems most reasonable. Masamune¹³⁰ reported a similar type of reaction (Equation 76) and claimed that the intermediate which was isolated, **49**, was of the same type as intermediate-2. However, no actual physical characterization of the intermediate was ever reported to substantiate the report.

The mechanism proposed in Equation 126 is not the same, however, as the one proposed earlier for the reaction of an amide with an α -halo ketone (Equation 122).¹⁶² That reaction was postulated to occur by initial attack by the amide oxygen on the halide ion (Equation 127) to give an iminoesters, **115**, which undergoes ring closure and loss of water to give the oxazole. A distinguishing feature of this alternative mechanism is the initial formation of imidate **115**. No evidence for an analogous intermediate in the reaction of **15b** with acetamide was obtained. Cyclization of **115** would provide an intermediate analogous to **47**, and the pathways become mechanistically similar.



Equation 127

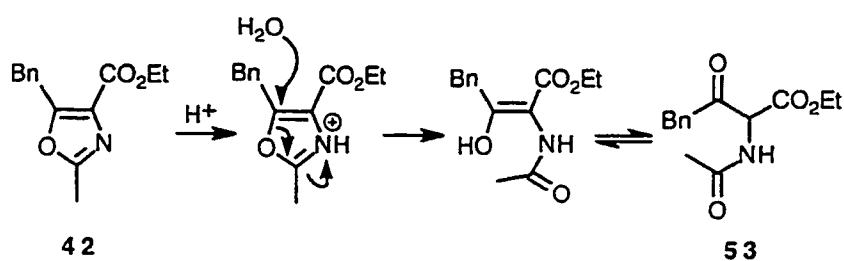
The structures of **46** and **47** were not immediately obvious. Moreover, **46** was the major intermediate, and only small amounts of **47** could be isolated under the best conditions. Qualitatively, it appeared that **47** was formed first but was converted to **46**, which was more stable and remained in solution longer. It was therefore important to establish the structure and regiochemistry of **46** and **47**, and identification of the product obtained from reduction of the intermediate was seen as a viable method for discriminating between **46** and **47** (Equation 77). Upon reduction, the C₂ methyl signal in the ¹H NMR was a singlet. Thus, **46** is 2-methyl-2-hydroxy-4-carboethoxy-5-benzyl-3-oxazolidine and has the hydroxyl group at C₂ as shown, indicating that the precursor to **51** is **46**. By inference, **47** has a hydroxyl group at C₄ and is 2-methyl-4-carboethoxy-4-hydroxy-5-benzyl-2-oxazoline, **47**.



Equation 77

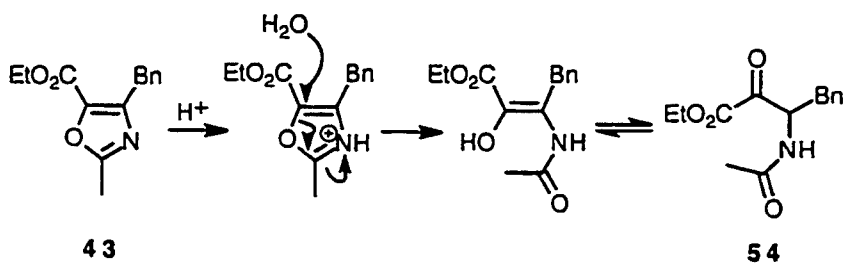
A final structural study was done to confirm the regiochemistry of the oxazole product **42**. Based on the mechanistic scenario (Equation 126), the expected structure is the 4-carboethoxy-5-benzyl regioisomer, **42**, as dictated by initial amide nitrogen addition to the ketone group of **15b**. To confirm this, acid promoted hydrolysis of the oxazole was carried out. If the oxazole

prepared was **42**, then water would add to C₅ and give ethyl 2-acetamido-3-oxo-4-phenylbutanoate, **53** (Equation 128). On the other hand, if the oxazole



Equation 128

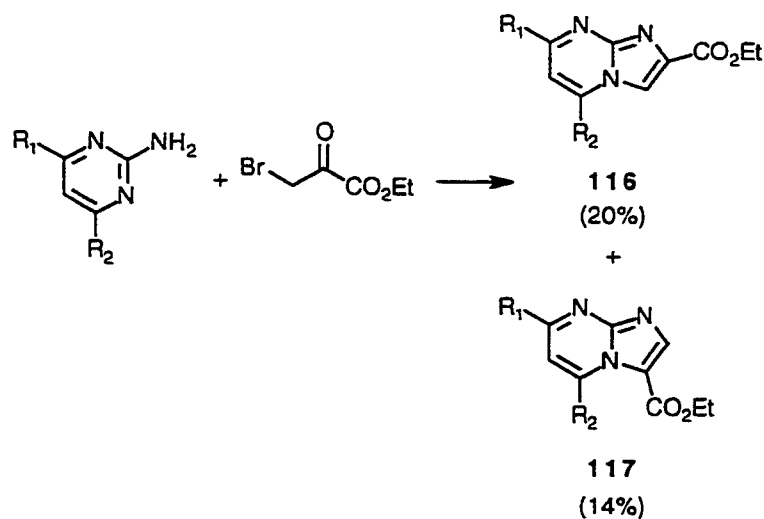
was regioisomer **43**, water would attack C₅ and give ethyl 3-acetamido-2-oxo-4-phenyl butanoate, **54**, (Equation 129). Hydrolysis of the oxazole product gave **53**; thus, the regiochemistry of the oxazole product is properly depicted as **42**. This further supports the general course of the reaction between **15b** and acetamide as shown (Equation 126).



Equation 129

In summary, the reaction of **15b** with acetamide provided the 4-carboethoxy oxazole **42** in good yields. There are a few reports of the

reaction of β -bromo- α -keto esters, also known as β -bromopyruvates with amides and heterocyclic amines. The reaction of β -bromopyruvates, with thioacetamide was found to give crude 4-carboethoxythiazoles in 65% yield.¹⁷² The reaction of β -bromopyruvates with amine heterocycles such as 2-amino pyridines was found to be much less selective, since the reaction provides both regioisomers, **116** (20%) and **117** (14%) (Equation 130.)^{173,174}



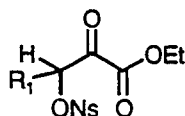
Equation 130

6. CONCLUSIONS

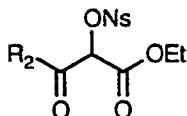
In pursuing the initial objective of this project, an effective synthesis for a variety of β -nosyloxy- α -keto esters from α -keto esters was developed. The first step in this process required the preparation of electron rich silyl enol ether derivatives of α -keto esters. The preparation of silyl enol ether derivatives was found to structure dependent, but regardless of the method utilized, all of the silyl enol ethers were prepared in good to excellent yields. Next, the electrophilic reagent, *p*-NBSP, was found to efficiently oxidize silyl enol ethers at the β -carbon to give β -nosyloxy- α -keto esters, **15**, in good overall yields.

A second objective of this work was to examine the viability of using β -nosyloxy- α -keto esters as synthetic intermediates to access other 1,2,3-trifunctionalized compounds. Two structural features of the β -nosyloxy- α -keto esters, the electrophilic carbonyl and the excellent leaving group ability of the nosylate group, were investigated. In exploring the carbonyl chemistry of β -nosyloxy- α -keto esters, **15**, it became clear that positioning the ketone group between the nosyloxy group and the ester group makes the ketone group extraordinarily electrophilic. Even poor nucleophiles such as water could easily add to the carbonyl. The ketone group was much more electrophilic than the isomeric β -keto- α -nosyloxy esters, **119**, which are extremely valuable synthetic intermediates.

Many normal carbonyl addition reagents, such as sodium borohydride or amines, caused deep-seated decomposition when reacted with **15**. Moreover, these compounds are also very base-sensitive and decompose in



15



118

their presence as well. Thus, many of the selective transformations originally envisioned for β -nosyloxy- α -keto esters were not feasible due to their extreme reactivity. Luckily, the carbonyl group of β -nosyloxy- α -keto esters reacted successfully with a range of very weak nucleophiles, such as water, sodium triacetoxyborohydride, amides and carbamates.

The nosylate group of **15** can be replaced by nucleophiles that have relatively low pK_a s such as azide ion and morpholine. It would appear that with respect to normal carbonyl and nosylate transformations, these materials are too reactive to be of wide-spread utility. However, in another respect, these compounds show significant synthetic potential. Because of their high reactivity, they can be treated with neutral amides or carbamates to give cyclocondensation products in high yields. With subsequent development, this could be the method of choice for the synthesis of several classes of important heterocycles, since the same type of reactions with β -halo- α -keto esters have been reported to give poor results with less regiocontrol. The extreme electrophilicity of the carbonyl group guides the regiochemistry by directing attack of the nucleophile to the carbonyl. It is envisioned that other carboxylic acid derivatives such as amidines and thioacids could provide entry to other classes of heterocycles as well.

7. EXPERIMENTAL SECTION

Most chemicals were purchased from Aldrich Chemical Company except for *p*-nitrobenzenesulfonyl chloride which was purchased from Fluka Chemical Co. and recrystallized from chloroform and hexane. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use, and acetone was distilled after stirring over CaSO₄. Acetonitrile, ether, triethylamine were dried with CaH₂ and distilled. Chlorotri-methylsilane was distilled from magnesium turnings. HPLC grade solvents were purchased from VWR.

¹H NMR and ¹³C NMR spectra were recorded on Varian 400 and 200 MHz spectrometers, and ¹³C NMR were recorded on Varian 400MHz spectrometer. Chemical shifts for both proton NMR spectra and ¹³C NMR spectra are reported for chloroform-*d* and acetone-*d*₆ solutions relative to TMS as an internal standard. IR spectra were determined on a Perkin-Elmer instrument. Melting points are uncorrected. Thin-layer chromatography was performed on silica gel 60 F₂₅₄ plates and visualized by UV irradiation and/or iodine. Analytical HPLC was performed with the indicated solvent systems and flow rates on a Rainin chromatograph equipped with a 21.4 mm ID x 25 cm L Dynamax 60A silica gel column and UV detector (254 nm). Flash chromatography was performed using silica gel 60 PF₂₅₄ containing gypsum. Radial chromatography was performed on a radial chromatograph (Harrison) using 1-mm and 2-mm layer of silica gel 60 PF₂₅₄ containing gypsum. Elemental analyses were carried out by M-H-W Laboratories, Phoenix, AZ.

1-Carbomethoxy-1-(trimethylsiloxy)ethylene, 11a. Methyl pyruvate, **10a**, (3.17 g, 31.1 mmol) was placed in a 3-neck flask fitted with an addition funnel. The system was purged with N₂, and tetrahydrofuran (60 mL) was syringed into the flask. Chlorotrimethylsilane (4.4 mL, 3.77 g, 35.0 mmol) was added to the flask, and triethylamine (5.85 mL, 4.25 g, 42.0 mmol) in tetrahydrofuran (40 mL) was added dropwise. After 3.5h, the tlc analysis of the reaction mixture (ethyl acetate/hexane; 1:4) showed little starting material. Pentane (75 mL) was added, and the reaction mixture was filtered. The filtrate was washed with water (2 x 50 mL) and with brine (1 x 50 mL). The organic layer was dried over MgSO₄ and evaporated to dryness. A clear liquid (3.63g, 67%) was obtained. No further purification of the product was attempted.: ¹H NMR (400 MHz, CDCl₃) δ 0.24 (s, 9H, OSi(CH₃)₃), 3.77 (s, 3H, O-CH₃), 4.88 (s, 1H, -C-H), 5.51 (s, 1H, -C-H); ¹³C NMR (400 MHz, CDCl₃) δ 0.3, 52.4, 104.3, 147.4, 165.2; IR (neat) 2956, 1735, 1627, 1439, 1329, 1254, 1200, 1168, 1029, 848 cm⁻¹.

1-Carboethoxy-1-(trimethylsiloxy)-3-phenylpropene, 11b. Ethyl 4-phenyl-2-oxobutylate, **10b**, (3.98 g, 19.0 mmol) was placed in a 3-neck flask fitted with an addition funnel. The system was purged with N₂, and tetrahydrofuran (40 mL) was syringed into the flask. Chlorotrimethylsilane (2.9 mL, 2.48 g, 23.0 mmol) was added to the flask, and triethylamine (3.75 mL, 2.72 g, 27.0 mmol) in tetrahydrofuran (20 mL) was added dropwise. After 3.5 h, the tlc analysis of the reaction mixture (ethyl acetate/hexane, 1:4) showed little starting material. Pentane (50 mL) was added, and the reaction mixture was filtered. The filtrate was washed with water (2 x 40 mL) and with

brine (1 x 40 mL). The organic layer was dried over MgSO_4 and evaporated to dryness. The crude product was separated by radial chromatography (ethyl acetate/hexane, 1:9) to afford (4.84 g, 89%) of the desired product.: ^1H NMR (400 MHz, CDCl_3) δ 0.25 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 1.29 (t, $J=7.2$ Hz, 3H, CH_3), 3.51 (d, $J=7.4$ Hz, 2H, $\text{Ph}-\text{CH}_2$), 4.20 (q, $J=7.2$ Hz, 2H, $\text{O}-\text{CH}_2$), 6.22 (t, $J=7.4$ Hz, 1H, $-\text{C}-\text{H}$), 7.19-7.21 (m, 3H, aromatic), 7.29-7.27 (m, 2H, aromatic); ^{13}C NMR (400 MHz, CDCl_3) δ 0.6, 14.2, 32.0, 61.0, 121.3, 126.2, 128.47, 128.52, 139.7, 141.0, 164.8; IR (neat) 3028, 2958, 2903, 1722, 1645, 1603, 1495, 1453, 1371, 1289, 1251, 1140, 843, 756 cm^{-1} .

1-Carboethoxy-1-(trimethylsiloxy)heptene, 11c. Ethyl 2-oxo-octanoate, **10c**, (3.59 g, 19.0 mmol) was placed in a 3-neck flask fitted with an addition funnel. The system was purged with N_2 , and tetrahydrofuran (40 mL) was syringed into the flask. Chlorotrimethylsilane (2.9 mL, 2.48 g, 23.0 mmol) was added to the flask, and triethylamine (3.75 mL, 2.72 g, 27.0 mmol) in tetrahydrofuran (20 mL) was added dropwise. After 3.5 h, pentane (50 mL) was added, and the reaction mixture was filtered. The filtrate was washed with water (2 x 40 mL) and with brine (1 x 40 mL). The organic layer was dried over MgSO_4 and evaporated to dryness. The crude product was separated by radial chromatography using an increasing polar solvent mixture (ethyl acetate/hexane; 2:98 to ethyl acetate/hexane, 1:9) to afford (2.46 g, 49%) of the desired product.: ^1H NMR (400 MHz, CDCl_3) δ 0.22 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 0.90 (t, $J=6.8$ Hz, 3H, CH_2-CH_3), 1.31 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.41 (t, $J=7.2$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.29-1.43 (m, 4H), 2.15 (dt, $J=7.2$, $J=7.6$ Hz, 2H, $\text{CH}-\text{CH}_2$), 4.21 (q, $J=7.2$ Hz, 2H, $-\text{OCH}_2$), 6.07 (t, $J=7.6$

Hz, 1H, CH); ^{13}C NMR (400 MHz, CDCl_3) δ 0.6, 14.2, 14.4, 22.7, 26.0, 28.6, 31.9, 61.0, 123.9, 140.8, 165.2; IR (neat) 2958, 2928, 1721, 1647, 1373, 1252, 1142, 1112, 848, 758 cm^{-1} .

1-Carboethoxy-1-(trimethylsiloxy)-2-methyl-2-carboethoxy-ethylene, 11d. Diethyloxalpropionate, **10d**, (2.95 g, 15.0 mmol) was placed in a 3-neck flask fitted with an addition funnel. The system was purged with N_2 , and tetrahydrofuran (35 mL) was syringed into the flask. Chlorotrimethylsilane (2.2 mL, 1.88 g, 17.0 mmol) was added to the flask, and triethylamine (2.90 mL, 2.11 g, 21.0 mmol) in tetrahydrofuran (15 mL) was added dropwise. After 3.5 h, pentane (50 mL) was added, and the reaction mixture was suction filtered and evaporated to dryness on the rotary evaporator using a vacuum (60 mm Hg). Purification by kugelrohr distillation (0.05-0.06 mm Hg) afforded a clear liquid (3.53 g) which contains the desired product (3.00 g, 74% yield) and diethyloxalpropionate (0.53g, 2.6 mmol).: ^1H NMR (400 MHz, CDCl_3) δ 0.26 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 1.28 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.34 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.84 (s, 3H, CH_3), 4.18 (q, $J=7.2$ Hz, 2H, $-\text{OCH}_2$), 4.25 (q, $J=7.2$ Hz, 2H, $-\text{OCH}_2$); ^{13}C NMR (400 MHz, CDCl_3) δ 0.7, 12.5, 14.3, 14.5, 61.0, 61.9, 115.4, 148.6, 165.6, 168.6; IR (neat) 2980, 1735, 1719, 1638, 1368, 1298, 1255, 1204, 1124, 1057, 852 cm^{-1} .

1-Carboethoxy-1-(trimethylsiloxy)-2-methylpropylene, 11e.

Potassium hydride (35 % by weight, 1.32g, 0.46 g actual, 11.5 mmol) was washed with pentane (3 x 5 mL) under N_2 . Dry tetrahydrofuran (25 mL) was added, and the flask was cooled to 0 $^\circ\text{C}$. Ethyl 3-methyl-2-oxobutylate, **10e**,

(1.55 g, 10.8 mmol) was syringed into the flask, and the reaction was allowed to stir for 30 minutes. The orange solution was syringed into a 3-neck flask fitted with an addition funnel. The system was purged with N₂, and chlorotrimethylsilane (3.0 mL, 2.57 g, 24 mmol) in tetrahydrofuran (15 mL) was added dropwise. After 2.5 h, pentane (50 mL) was added, and the reaction mixture was suction filtered and evaporated to dryness on the rotary evaporator using a vacuum (60 mm Hg). Purification by kugelrohr distillation (0.05-0.06 mm Hg) afforded a clear liquid (1.81 g) which was a mixture of the desired product (1.64 g, 71% yield) and ethyl 3-methyl-2-oxobutyrates (0.17 g, 1.2 mmol).: ¹H NMR (400 MHz, CDCl₃) δ 0.19 (s, 9H, Si(CH₃)₃), 1.33 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.80 (s, CH₃), 2.06 (s, CH₃), 4.21 (q, J=7.2 Hz, 2H, -OCH₂); ¹³C NMR (400 MHz, CDCl₃) δ 0.4, 14.3, 19.7, 20.6, 60.4, 130.6, 135.8, 165.2; IR (neat) 2958, 2908, 1717, 1637, 1290, 1251, 1230, 1187, 1080, 883, 846, 757 cm⁻¹.

1-Carboethoxy-1-(trimethylsiloxy)-2-cyclohexylethylene, 11f.

Potassium hydride (35 % by weight, 0.83 g, 0.29 g actual, 7.2 mmol) was washed with pentane (3 x 5 mL) under N₂. Dry tetrahydrofuran (25 mL) was added, and the flask was cooled to 0 °C. Ethyl cyclohexylglyoxylate, **10f**, (1.14 g, 6.2 mmol) was syringed into the flask, and the reaction was allowed to stir for 40 minutes. The orange solution was syringed into a 3-neck flask fitted with an addition funnel. The system was purged with N₂, and chlorotrimethylsilane (1.5 mL, 1.28 g, 12.0 mmol) in tetrahydrofuran (15 mL) was added dropwise. After 2.5h, pentane (50 mL) was added, and the reaction mixture was suction filtered and evaporated to dryness on a rotary

evaporator using a vacuum (60 mm Hg). Purification by kugelrohr distillation (0.05-0.06 mm Hg) afforded a clear liquid (1.15 g, 72%). The crude mixture was not completely pure, but no further purification was attempted.: ^1H NMR (400 MHz, CDCl_3) δ 0.18 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 1.33 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.57 (m, 6H, CH_2), 2.28 (m, 2H, CH_2), 2.64 (m, 2H, CH_2), 4.20 (q, $J=7.2$ Hz, 2H, $-\text{OCH}_2$); ^{13}C NMR (400 MHz, CDCl_3) δ 0.5, 14.5, 26.7, 27.7, 28.3, 29.3, 29.4, 60.6, 133.3, 137.2, 165.8; IR (neat) 2929, 2855, 1716, 1630, 1450, 1283, 1251, 1226, 1152, 1101, 877, 846, 757 cm^{-1} .

γ -Lactone, 14. Potassium hydride (35 % by weight, 1.38g, 0.48 g actual, 12.0 mmol) was washed with pentane (3 x 5 mL) under N_2 . Dry tetrahydrofuran (30 mL) was added, and the flask was cooled to 0 $^\circ\text{C}$. Ethyl 2-oxo-octanoate, **10c**, (1.86 g, 10.0 mmol) dissolved in tetrahydrofuran (10 mL) was added, and the reaction was allowed to stir for 30 minutes. The orange solution was syringed into a 3-neck flask fitted with an addition funnel. The system was purged with N_2 , and chlorotrimethylsilane (2.5 mL, 2.14 g, 19.7 mmol) in tetrahydrofuran (10 mL) was added dropwise. After 3.0h, pentane (30 mL) was added, and the reaction mixture was suction filtered and evaporated to dryness on the rotary evaporator using a vacuum (60 mm Hg). Removal of the volatile impurities by kugelrohr distillation (0.05-0.06 mm Hg) left sticky, yellow oil (1.31 g, 80%) in the distillation bulb. Alternatively, after the filtration, the filtrate was washed with water (2 x 25 mL) and with brine (1 x 25 mL). The organic layer was dried over MgSO_4 and evaporated to dryness to afford a dark orange oil. Purification of the crude product by radial chromatography (ethyl acetate/hexane, 5:95) afforded (0.87 g, 53 %) the

lactone.: ^1H NMR (400 MHz, CDCl_3) δ 0.87 (t, $J=7.2$ Hz, 3H, CH_3), 0.90 (t, $J=7.2$ Hz, 3H, CH_3), 1.28 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.26-1.32 (m, 12H, CH_2), 1.53-1.65 (m, 2H, CH_2), 1.81-1.88 (m, 1H, CHH), 2.19-2.27 (m, 2H, CH_2), 2.30-2.38 (m, 1H, CHH), 4.21 (q, $J=7.2$ Hz, 2H, OCH_2); ^{13}C NMR (400 MHz, CDCl_3) δ 13.97, 14.02, 14.06, 22.3, 22.5, 22.8, 24.5, 26.2, 29.0, 31.5, 31.9, 34.0, 62.4, 87.8, 133.9, 138.7, 168.7, 170.3; IR (neat) 3337, 2957, 2932, 2860, 1765, 1737, 1701, 1467, 1393, 1252, 1183, 1116, 1029 cm^{-1} .

Methyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-propionate, 15a. To a cooled solution (0°C) of 1-carbomethoxy-1-(trimethylsiloxy)-ethylene, **11a**, (0.41 g, 2.4 mmol) in ethyl acetate (40 mL) was added *p*-NPSP (0.61 g, 1.5 mmol). The mixture was allowed to stir for 4h at 0°C . After 4h, the reaction was placed in the refrigerator overnight. The reaction mixture turned a pale yellow with a small amount of white precipitate. The solution was washed with cold water (2 x 25 mL) and once with brine (1 x 25 mL). The organic layer was dried over MgSO_4 and evaporated until 10 mL of liquid remained. Hexane was added until cloudy, and the solution was evaporated to dryness to afford a pale yellow solid. Recrystallization from ethyl acetate/hexane gave a pale yellow solid (0.375 g, 82%). : m.p. $118-120^\circ$ (dec.); ^1H NMR (400 MHz, CDCl_3) δ 3.92 (s, 3H, OCH_3), 5.34' (s, 2H, CH_2ONs), 8.18 and 8.43 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^1H NMR (400 MHz, acetone- d_6) δ 3.84 (s, 3H, OCH_3), 5.49 (s, 2H, CH_2ONs), 8.28 and 8.52 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 53.7, 71.2, 124.5, 129.5, 141.5, 151.1, 158.9, 183.8; ^{13}C NMR (400 MHz, acetone- d_6) δ 53.3, 72.9, 125.5, 130.5, 142.2, 152.1, 159.7, 184.4; IR (KBr) 3110, 2962, 2925, 1764, 1609,

1529, 1370, 1356, 1267, 1190, 1001, 822, 746 cm^{-1} ; Analysis calc'd for $\text{C}_{10}\text{H}_9\text{NO}_8\text{S}$: C, 39.61; H, 2.99; N, 4.62; found: C, 39.76; H, 2.75; N, 4.42.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-4-phenylbutanoate,

15b. To a cooled solution (0°C) of 1-carboethoxy-1-(trimethylsiloxy)-3-phenylpropene, **11b**, (0.60g, 2.2 mmol) in ethyl acetate (40 mL) was added *p*-NPSP (0.66 g, 1.6 mmol). The mixture was allowed to stir for 4h at 0°C . After 4h, the reaction was placed in the refrigerator overnight. The reaction mixture turned a pale yellow with a small amount of white precipitate. The solution was washed with cold water (2 x 25 mL) and once with brine (1 x 25 mL). The organic layer was dried over MgSO_4 and evaporated until 10 mL of liquid remained. Hexane was added until cloudy, and the solution was evaporated to dryness to afford a pale yellow solid. Recrystallization from ethyl acetate/hexane afforded a white solid (0.55g, 81%): m.p. $104\text{--}105^\circ$; ^1H NMR (400 MHz, CDCl_3) δ 1.40 (t, $J=7.2$ Hz, 3H, CH_3), 3.00 (dd, $J=10.0$, $J=14.2$ Hz, 1H, Ph-CH_2), 3.27 (dd, $J=3.6$, $J=14.2$ Hz, 1H, Ph-CH_2), 4.37 (q, $J=7.2$ Hz, 2H, CH_2), 5.63 (dd, $J=3.6$, $J=10.0$ Hz, 1H, CHONs), 7.05-7.07 (m, 2H, aromatic CH), 7.14-7.21 (m, 3H, aromatic CH), 7.75 and 8.16 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^1H NMR (400 MHz, acetone- d_6) δ 1.37 (t, $J=7.2$ Hz, 2H, CH_3), 2.99 (dd, $J=10.0$, $J=14.5$ Hz, 1H, Ph-CH_2), 3.41 (dd, $J=3.2$, $J=14.5$ Hz, 1H, Ph-CH_2), 4.39 (q, $J=7.2$ Hz, 2H, CH_2), 5.72 (dd, $J=3.2$, $J=10.0$ Hz, 1H, CHONs), 7.11 (m, 2H, aromatic CH), 7.15-7.16 (m, 3H, aromatic CH), 7.87 and 8.27 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 12.9, 36.1, 62.4, 81.6, 123.2, 126.5, 127.8, 127.9, 128.3, 132.9, 139.9, 149.5, 158.5, 186.3; ^{13}C NMR (400 MHz, acetone- d_6) δ 14.1, 37.5,

63.8, 84.0, 125.4, 128.0, 129.5, 130.0, 130.2, 135.5, 141.6, 151.8, 160.2, 188.3; IR (KBr) 3027, 2919, 1766, 1724, 1603, 1531, 1382, 1350, 1187, 1095, 1014, 699 cm^{-1} ; Analysis calc'd for $\text{C}_{18}\text{H}_{17}\text{NO}_8\text{S}$: C, 53.07; H, 4.21; N, 3.44; found: C, 52.88; H, 4.40; N, 3.24.

Ethyl 3-(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-octanoate, 15c. To a cooled solution (0°C) of 1-carboethoxy-1-(trimethylsiloxy)-1-heptene, 11c, (0.50 g, 1.9 mmol) in ethyl acetate (40 mL) was added *p*-NPSP (0.65g, 1.6 mmol). The mixture was allowed to stir for 4h at 0°C . After 4h, the reaction was placed in the refrigerator overnight. The reaction mixture turned a pale yellow with a small amount of white precipitate. The solution was washed with cold water (2 x 25 mL) and once with brine (1 x 25 mL). The organic layer was dried over MgSO_4 and evaporated until 10 mL of liquid remained. Hexane was added until cloudy, and the solution was evaporated to dryness to afford a pale yellow oil. The yellow oil was separated using radial chromatography. A stepped, non-polar to polar, solvent system of ethyl acetate/hexane (1: 4) to ethyl acetate/hexane (1: 1) was used to afford a pale yellow oil (0.55 g, 88 %): ^1H NMR (400 MHz, CDCl_3) δ 0.85 (t, 3H, $J=6.4$, CH_2-CH_3), 1.26 (m, 4H, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.25-1.27 (m (buried), 2H), 1.38 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.78-1.87 (m, 1H, $\text{CH}(\text{ONs})\text{CH}_2$), 1.91-2.00 (m, 1H, $\text{CH}(\text{ONs})\text{CH}_2$), 4.36 (q, $J=7.2$ Hz, 2H, OCH_2), 5.65 (dd, $J=4.0$, $J=8.4$ Hz, 1H, CHONs), 8.15 and 8.42 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^1H NMR (400 MHz, acetone- d_6) δ 0.81 (t, 3H, $J=6.4$, CH_2-CH_3), 1.20-1.28 (m, 6H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$), 1.33 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.79-1.88 (m, 1H, $\text{CH}(\text{ONs})\text{CH}_2$), 1.97-2.05 (m, 1H, $\text{CH}(\text{ONs})\text{CH}_2$), 4.34 (q, $J=7.2$ Hz, 2H,

OCH₂), 5.64 (dd, J=3.4, J=8.2 Hz, 1H, CHONs), 8.28 and 8.54 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 13.8, 13.9, 22.2, 24.4, 30.78, 30.81, 63.3, 81.9, 124.4, 129.4, 141.8, 150.9, 159.5, 188.0; ¹³C NMR (400 MHz, acetone-d₆) δ 14.0, 14.1, 22.8, 24.9, 31.3, 31.4, 63.6, 83.0, 125.6, 130.4, 142.3, 152.0, 160.3, 188.8; IR (neat) 3109, 2958, 2933, 2871, 1756, 1731, 1608, 1535, 1380, 1351, 1312, 1188, 1094, 942, 853, 618 cm⁻¹; Analysis calc'd for C₁₆H₂₁NO₈S: C, 49.61; H, 5.46; N, 3.62; found: C, 49.48; H, 5.59; N, 3.59.

Ethyl 3-carboethoxy-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-butanoate, 15d. To a cooled solution (0 °C) of 1-carboethoxy-1-(trimethylsiloxy)-3-carboethoxypropene, 11d, (0.91g, 3.3 mmol) in ethyl acetate (50 mL) was added *p*-NPSP (0.63g, 1.6 mmol). The mixture was allowed to stir for 4h at 0 °C. After 4h, the reaction was placed in the refrigerator overnight. The reaction mixture turned a pale yellow with a small amount of white precipitate. The solution was washed with cold water (2 x 25 mL) and once with brine (1 x 25 mL). The organic layer was dried over MgSO₄ and evaporated until 10 mL of liquid remained. Hexane was added until cloudy, and the solution was evaporated to dryness to afford a pale yellow oil. The oil was dissolved in ethyl acetate, and hexane was added until cloudy. A pale yellow oil (0.41g, 65%) was collected.: ¹H NMR (400 MHz, CDCl₃) δ 1.28 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.36 (t, J=7.2 Hz, 3H, OCH₂CH₃), 2.00 (s, 3H, CH₃), 4.30 (q, 2H, J=7.2, OCH₂), 4.33-4.39 (m, 2H, OCH₂), 8.16 and 8.42 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ¹H NMR (400 MHz, acetone-d₆) δ 1.25 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.33 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.94 (s, 3H,

CH₃), 4.26-4.32 (m, 2H, OCH₂), 4.35-4.41 (m, 2H, OCH₂), 8.26 and 8.56 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 13.8, 13.9, 21.2, 63.4, 63.5, 88.7, 124.4, 129.2, 143.0, 150.9, 159.6, 165.2, 184.4; ¹³C NMR (400 MHz, acetone-d₆) δ 14.0, 14.1, 21.1, 64.0, 64.1, 89.4, 125.7, 129.9, 143.6, 152.1, 160.1, 165.6, 185.2; IR (neat) 3110, 2987, 1759, 1737, 1609, 1537, 1371, 1352, 1192, 1085, 1035, 941, 856, 745 cm⁻¹; Analysis calc'd for C₁₅H₁₇NO₁₀S: C, 44.67; H, 4.25; N, 3.47; found: C, 44.82; H, 4.02; N, 3.41.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-3-methylbutanoate,

15e. To a cooled solution (0 °C) of 1-carboethoxy-1-(trimethylsiloxy)-2-methylpropylene, **11e**, (0.36g, 1.7 mmol) in ethyl acetate (40 mL) was added *p*-NPSP (0.61 g, 1.5 mmol). The mixture was allowed to stir for 4h at 0 °C. After 4h, the reaction was placed in the refrigerator overnight. The reaction mixture turned a pale yellow with a small amount of white precipitate. The solution was washed with cold water (2 x 25 mL) and once with brine (1 x 25 mL). The organic layer was dried over MgSO₄ and evaporated until 10 mL of liquid remained. Hexane was added until cloudy, and the solution was evaporated to dryness to afford an off-white solid. Recrystallization from ethyl acetate/hexane gave of an off-white solid (0.32g, 61%). : m.p. 66-68° (dec.); ¹H NMR (400 MHz, CDCl₃) δ 1.38 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.83 (s, 6H, CH₃), 4.36 (q, J=7.2 Hz, 2H, OCH₂), 8.14 and 8.41 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ¹H NMR (400 MHz, acetone-d₆) δ 1.33 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.79 (s, 6H, CH₃), 4.37 (q, J=7.2 Hz, 2H, OCH₂), 8.25 and 8.54 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 14.0,

25.2, 62.9, 91.8, 124.4, 129.0, 143.5, 150.7, 160.5, 191.5; ^{13}C NMR (400 MHz, acetone- d_6) δ 14.2, 25.2, 63.4, 92.6, 125.6, 129.8, 144.4, 151.9, 161.5, 192.5; IR (KBr) 3116, 2993, 1739, 1607, 1532, 1363, 1350, 1304, 1235, 1186, 1132, 1091, 1051, 894 cm^{-1} ; Analysis calc'd for $\text{C}_{13}\text{H}_{15}\text{NO}_8\text{S}$: C, 45.22; H, 4.38; N, 4.06; found: C, 45.12; H, 4.42; N, 4.11.

Ethyl 3-(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-3-cyclohexyl-propionate, 15f. To a cooled solution (0 °C) of 1-carboethoxy-1-(trimethylsiloxy)-2-cyclohexylethylene, 11f, (0.41 g, 1.6 mmol) in ethyl acetate (40 mL) was added *p*-NPSP (0.61 g, 1.5 mmol). The mixture was allowed to stir for 4h at 0 °C. After 4h, the reaction was placed in the refrigerator overnight. The reaction mixture turned a pale yellow with a small amount of white precipitate. The solution was washed with cold water (2 x 25 mL) and once with brine (1 x 25 mL). The organic layer was dried over MgSO_4 and evaporated until 10 mL of liquid remained. Hexane was added until cloudy, and the solution was evaporated to dryness to afford a white solid.

Recrystallization from ethyl acetate/hexane gave a white solid (0.34 g, 59%). : m.p. 103-105°; ^1H NMR (400 MHz, CDCl_3) δ 1.26-1.35 (m, 1H, CHH), 1.39 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.55-1.69 (m, 5H, $\text{CH}_2\text{CHHCH}_2$), 1.98 (dt, $J=3.6$, $J=13.2$ Hz, 2H, CH_2), 2.40 (d, $J=14.0$ Hz, 2H, CH_2), 4.36 (q, $J=7.2$ Hz, 2H, OCH_2), 8.17 and 8.42 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^1H NMR (400 MHz, acetone- d_6) δ 1.30-1.35 (m, 1H, CHH), 1.32 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.50-1.65 (m, 5H, $\text{CH}_2\text{CHHCH}_2$), 1.98 (dt, $J=4.0$, $J=13.2$ Hz, 2H, CH_2), 2.36 (d, $J=14.0$ Hz, 2H, CH_2), 4.33 (q, $J=7.2$ Hz, 2H, OCH_2), 8.28 and 8.55 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ

14.0, 20.9, 24.3, 32.8, 62.8, 94.3, 124.3, 129.1, 143.3, 150.7, 160.3, 191.5;
 ^{13}C NMR (400 MHz, acetone- d_6) δ 14.2, 21.6, 24.9, 33.3, 63.2, 94.9, 125.6,
129.9, 144.1, 152.0, 161.1, 192.2; IR (KBr) 3104, 2943, 2873, 1740, 1605,
1538, 1361, 1348, 1231, 1185, 1150, 189, 1018, 939, 888, 738 cm^{-1} ; Analysis
calc'd for $\text{C}_{16}\text{H}_{19}\text{NO}_8\text{S}$: C, 49.87; H, 4.97; N, 3.63; found: C, 49.92; H, 5.11;
N, 3.59.

Ethyl 3-(*p*-nitrobenzenesulfonyl)oxy]-3-phenyl-2-oxopropionate,

15g. Dry zinc chloride (0.21 g, 1.5 mmol) and *p*-NPSP (0.60 g, 1.5 mmol) were placed in ethyl acetate (50 mL), and the suspension was allowed to stir for 20 minutes at 0 °C until the solution turned clear. Ethyl 3-phenylpyruvate, **10g**, (0.37 g, 1.9 mmol) was added, and the mixture was allowed to stir for 4 h at 0 °C. After 4h, the reaction was placed in the refrigerator overnight. The reaction mixture turned a pale yellow with a small amount of white precipitate. The solution was washed with cold water (2 x 25 mL) and once with brine (1 x 25 mL). The organic layer was dried over MgSO_4 and evaporated until 10 mL of liquid remained. Hexane was added to the solution until cloudy, and the solution was evaporated to dryness to afford an orange solid. Recrystallization from ethyl acetate/hexane gave a yellow solid (0.39 g, 67%). : m.p. 105-107°; ^1H NMR (400 MHz, CDCl_3) δ 1.26 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 4.22 (dq, $J=7.2, 10.6$ Hz, 1H, OCH_2H), 4.27 (dq, $J=7.2, 10.6$ Hz, 1H, OCH_2H), 6.71 (s, 1H, $\text{CH}(\text{ONs})$), 7.26-7.37 (m, 5H, aromatic CH), 8.00 and 8.28 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^1H NMR (400 MHz, acetone- d_6) δ 1.21 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 4.20 (dq, $J=7.2, J=10.2$ Hz, 1H, OCH_2), 4.25 (dq, $J=7.2, J=10.2$ Hz, 1H, OCH_2), 6.81 (s, 1H, $\text{CH}(\text{ONs})$), 7.32-7.40 (m, 5H, aromatic

CH), 8.10 and 8.38 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 13.8, 63.3, 83.2, 124.2, 129.1, 129.2, 129.29, 129.33, 130.7, 142.3, 150.7, 159.0, 184.3; ^{13}C NMR (400 MHz, acetone- d_6) δ 14.0, 63.6, 84.6, 125.3, 128.3, 130.00, 130.04, 130.3, 131.2, 142.9, 151.8, 159.7, 185.2; IR (KBr) 3109, 2957, 1752, 1740, 1609, 1538, 1379, 1353, 1191, 1076, 951, 850, 742, 626 cm^{-1} ; Analysis calc'd for $\text{C}_{17}\text{H}_{15}\text{NO}_8\text{S}$: C, 51.91; H, 3.84; N, 3.56; found: C, 51.96; H, 4.00; N, 3.50.

Methyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-dihydroxy-propionate,

16a. The NMR of methyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-propionate, **15a**, in acetone- d_6 was measured at regular time intervals after D_2O (drop) was added. After 15 minutes, the ^1H NMR showed **15a** was (99%) hydrated.: ^1H NMR (400 MHz, acetone- d_6) δ 3.72 (s, 3H, OCH_3), 4.28 (s, 2H, CH_2ONs), 8.24 and 8.54 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ^{13}C NMR (400 MHz, acetone- d_6) δ 53.2, 73.3, 92.4, 125.4, 130.4, 141.8, 151.8, 170.6.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-dihydroxy-4-

phenylbutanoate, 16b. The NMR of ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-4-phenylbutanoate, **15b**, was measured at regular time intervals after D_2O (drop) was added. After 30 minutes, the ^1H NMR showed **15b** was (96%) hydrated.: ^1H NMR (400 MHz, acetone- d_6) δ 1.32 (t, J=7.2 Hz, 3H, CH_3), 2.92 (dd, J=10.2, J=14.8 Hz, 1H, Ph- CH_2), 3.23 (dd, J=2.0, J=14.8 Hz, 1H, Ph- CH_2), 4.13 (d, J=4.6 Hz, 2H, OH_2), 4.21 (dq, J=4.6, J=7.2 Hz, 2H, CH_2), 5.29 (dd, J=2.0, J=10.2 Hz, 1H, CHONs), 7.07-7.16 (m, 5H, aromatic CH), 7.71 and 8.24 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ^{13}C NMR (400

MHz, acetone- d_6) δ 14.1, 35.7, 63.0, 88.3, 94.1, 124.9, 127.3, 129.2, 129.4, 130.3, 137.4, 143.7, 151.0, 170.9.

Ethyl 3-(*p*-nitrobenzenesulfonyl)oxy]-2-dihydroxyoctanoate, 16c.

The NMR of ethyl 3-(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-octanoate, **15c**, was measured at regular time intervals after D₂O (drop) was added. After 240 minutes, the ¹H NMR showed **15c** was (86%) hydrated.: ¹H NMR (400 MHz, acetone- d_6) δ 0.86 (t, 3H, *J*=6.8, CH₂-CH₃), 1.23-1.35 (m, 6H, CH₃CH₂CH₂CH₂), 1.25 (t, *J*=7.2 Hz, 3H, OCH₂CH₃), 1.76-1.88 (m, 2H, CH(ONs)CH₂), 4.10 (dq, *J*=7.2, *J*=10.8 Hz, 1H, OCH₂), 4.19 (dq, *J*=7.2, *J*=10.8 Hz, 1H, OCH₂), 4.98 (dd, *J*=3.6, *J*=9.0 Hz, 1H, CHONs), 8.21 and 8.47 (AA'BB', *J*=8.8 Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, acetone- d_6) δ 14.12, 14.15, 22.9, 25.8, 29.7, 31.9, 62.7, 87.4, 94.2, 124.9, 130.0, 144.2, 151.3, 170.9.

Ethyl 3-carboethoxy-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-dihydroxy-butanoate, 16d. The NMR of ethyl 3-carboethoxy-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-butanoate, **15d**, was measured at regular time intervals after D₂O (drop) was added. After 120 minutes, the ¹H NMR showed **15d** was (84%) hydrated.: ¹H NMR (400 MHz, acetone- d_6) δ 1.16 (t, *J*=7.2 Hz, 3H, OCH₂CH₃), 1.28 (t, *J*=7.2 Hz, 3H, OCH₂CH₃), 1.95 (s, 3H, CH₃), 4.14-4.20 (m, 2H, OCH₂), 4.26 (q, 2H, *J*=7.2, OCH₂), 8.28 and 8.53 (AA'BB', *J*=8.8 Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, acetone- d_6) δ 14.0, 14.1, 18.2, 63.1, 63.2, 92.2, 95.3, 125.2, 129.7, 144.7, 151.5, 168.5, 170.0.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-dihydroxy-3-methylbutanoate, 16e. The NMR of ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-3-methylbutanoate, 15e, in acetone- d_6 was measured at regular time intervals after D_2O (drop) was added. After 60 minutes, the 1H NMR showed 15e was (71%) hydrated, however, the elimination product and other unidentified side products were seen after 15 minutes. More decomposition occurred with time.: 1H NMR (400 MHz, acetone- d_6) δ 1.22 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.72 (s, 6H, CH_3), 4.21 (q, $J=7.2$ Hz, 2H, OCH_2), 8.21 and 8.50 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^{13}C NMR (400 MHz, acetone- d_6) δ 14.2, 22.4, 62.9, 96.1, 97.2, 125.3, 129.6, 145.8, 151.4, 171.4.

Ethyl 3-cyclohexene-2-oxo-acetate, 17. The NMR of ethyl 3-(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-3-cyclohexylpropionate, 15f, in acetone- d_6 was measured at regular time intervals after D_2O was added. After 48 h, the 1H NMR showed 15f had decomposed.: 1H NMR (400 MHz, acetone- d_6) δ 1.329 (t, $J=7.2$ Hz, 3H, CH_3), 1.671 (t, $J=2.8$ Hz, 4H, CH_2CH_2), 2.198 (br s, 2H, CH_2), 2.348 (br s, 2H, CH_2), 4.334 (q, $J=7.2$ Hz, 2H, OCH_2), 6.986 (t, $J=3.6$ Hz, 1H, $CH=C$); ^{13}C NMR (400 MHz, acetone- d_6) δ 14.3, 22.18, 22.20, 22.6, 27.2, 62.6, 136.6, 150.6, 166.1, 189.8.

Ethyl 3-(*p*-nitrobenzenesulfonyl)oxy]-3-phenyl-2-dihydroxypropionate, 16g. The NMR of ethyl 3-(*p*-nitrobenzenesulfonyl)oxy]-3-phenyl-2-oxopropionate, 15g, in acetone- d_6 was measured at regular time intervals after D_2O (drop) was added. After 45 minutes, the 1H NMR showed 15g was (97%) hydrated.: 1H NMR (400 MHz, acetone- d_6) δ 1.28 (t, $J=7.2$ Hz, 3H,

OCH₂CH₃), 4.18 (q, J=7.2 Hz, 2H, OCH₂), 5.81 (s, 1H, CH(ONs)), 7.13-7.22 (m, 3H, aromatic CH), 7.33 (d, J=7.2 Hz, 2H, aromatic CH), 7.92 and 8.25 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, acetone-d₆) δ 14.2, 62.9, 86.6, 94.5, 124.9, 128.3, 129.6, 130.2, 130.5, 133.2, 143.4, 151.3, 170.8.

Methyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxy-propionate, 18a.

Methyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-propionate, **15a**, (0.41 g, 1.4 mmol) was dissolved in tetrahydrofuran (40 mL) and cooled to 0 °C. Sodium triacetoxyborohydride (0.32 g, 1.5 mmol) was added, and the reaction mixture was allowed to stir for 18 h at room temperature. Ethyl acetate (40 mL) was added, and the reaction mixture was washed with water (3 x 40 mL) and with brine (1 x 40 mL). The aqueous layers were washed with ethyl acetate, and the combined organic layers were dried over MgSO₄, passed over a pad of silica gel, and evaporated to give a yellow oil. Recrystallization from ethyl acetate/hexane afforded a yellow solid (0.25 g, 61%): m.p. 80-82°; ¹H NMR (400 MHz, CDCl₃) δ 3.83 (s, 3H, OCH₃), 4.40 (t, J=2.8 Hz, 1H, CHOH), 4.44 (d, J=2.8 Hz, 2H, CH ONs), 8.12 and 8.41 (AA'BB', J=8.4 Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 53.4, 69.0, 71.4, 124.4, 129.4, 141.4, 150.9, 171.1; IR (KBr) 3514, 3118, 2968, 1735, 1610, 1543, 1367, 1351, 1255, 1181, 1131, 975, 929, 778, 617 cm⁻¹; Analysis calc'd for C₁₀H₁₁NO₈S: C, 39.35; H, 3.63; N, 4.59; found: C, 39.51; H, 3.75; N, 4.58.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxy-4-phenyl-butanoate, 18b. Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-4-phenyl-

butanoate, **15b**, (0.35 g, 0.86 mmol) was dried by toluene reflux. After evaporation of the toluene, tetrahydrofuran (40 mL) was added, and the solution was cooled to 0°C. Sodium triacetoxyborohydride borohydride (0.21 g, 0.99 mmol) was added, and the mixture was allowed to stir for 11 h at room temperature. Ethyl acetate (40 mL) was added, and the reaction mixture was washed with water (3 x 40 mL) and with brine (1 x 40 mL). The aqueous layers were washed with ethyl acetate, and the combined organic layers were dried over MgSO₄, passed over a pad of silica gel, and evaporated to give a yellow oil. Recrystallization from ethyl acetate/hexane afforded a pale, yellow solid (0.27 g, 77 %): m.p. 73-74°; ¹H NMR (400 MHz, CDCl₃) δ 1.32 (t, J=7.2 Hz, 3H, OCH₂CH₃), 3.05 (dd, J=7.4, J=13.8 Hz, 1H, Ph-CH₂H), 3.16 (dd, J=7.4, J=13.8 Hz, 1H, Ph-CH₂H), 4.19 (dq, J=7.2, J=10.6 Hz, 1H, OCH₂H), 4.21 (dd, J=2.2, J=4.2 Hz, 1H, CHOH), 4.27 (dq, J=7.2, J=10.6 Hz, 1H, OCH₂H), 5.23 (ddd, J=2.2, J=7.4, J=7.4 Hz, 1H, CHONs), 7.16-7.22 (m, 5H, aromatic CH), 7.83 and 8.24 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ¹H NMR (400 MHz, acetone-d₆) δ 1.22 (t, J=7.2 Hz, 3H, OCH₂CH₃), 3.01 (dd, J=7.4, J=13.6 Hz, 1H, Ph-CH₂H), 3.23 (dd, J=7.4, J=13.6 Hz, 1H, Ph-CH₂H), 4.03 (dq, J=7.2, J=10.6 Hz, 1H, OCH₂H), 4.12 (dq, J=7.2, J=10.6 Hz, 1H, OCH₂H), 4.23 (dd, J=2.2, J=7.2 Hz, 1H, CHOH), 4.78 (d, J=7.2 Hz, 1H, CHOH), 5.19 (ddd, J=2.2, J=7.4, J=7.4 Hz, 1H, CHONs), 7.19-7.22 (m, 5H, aromatic CH), 8.01 and 8.39 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 14.0, 37.3, 62.9, 70.7, 84.2, 124.2, 127.3, 128.82, 128.84, 129.6, 135.0, 142.2, 150.5, 171.4; IR (KBr) 3491, 3129, 3001, 1743, 1608, 1527, 1373, 1350, 1252, 1189, 1108, 1016, 901, 855, 758, 629 cm⁻¹; Analysis calc'd for C₁₈H₁₉NO₈S: C, 52.81; H, 4.68; N, 3.42; found: C, 52.90; H, 4.69; N, 3.38.

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxy-4-octanoate, 18c.

Ethyl 3-(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxy-4-octanoate, **15c**, (0.33 g, 0.85 mmol) was dissolved in tetrahydrofuran (40 mL), and the mixture was cooled to 0°C. Sodium triacetoxyborohydride (0.20 g, 0.94 mmol) was added, and the mixture was allowed to stir overnight at room temperature. Ethyl acetate (40 mL) was added, and the reaction mixture was washed with water (3 x 40 mL) and with brine (1 x 40 mL). The aqueous layers were washed with ethyl acetate, and the combined organic layers were dried over MgSO₄, passed over a pad of silica gel, and evaporated to give an orange oil. Using radial chromatography (ethyl acetate:hexane, 1:4), the crude was purified to give a yellow oil (0.23 g, 70%): ¹H NMR (400 MHz, CDCl₃) δ 0.87 (t, J=6.4 Hz, 3H, CH₂CH₃), 1.27-1.35 (m, 6H, CH₂CH₂CH₂CH₃), 1.33 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.72-1.81 (m, 1H, CHHCH(ONs)), 1.82-1.91 (m, 1H, CHHCH(ONs)), 2.99 (br s, 1H, CHOH), 4.19 (dq, J=7.2, J=10.6 Hz, 1H, OCHH), 4.26 (d, J=2.0 Hz, 1H, CHOH), 4.29 (dq, J=7.2, J=10.6 Hz, 1H, OCHH), 5.06 (ddd, J=2.0, J=7.4, J=7.4 Hz, 1H, CHONs), 8.09 and 8.39 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 13.9, 14.0, 22.4, 24.8, 31.0, 31.3, 62.8, 71.2, 83.7, 124.3, 129.1, 142.7, 150.7, 171.6; IR (neat) 3493, 3109, 2957, 2933, 2872, 1742, 1608, 1535, 1351, 1186, 1096, 904, 854, 746 cm⁻¹; Analysis calc'd for C₁₆H₂₃NO₈S: C, 49.35; H, 5.95; N, 3.60; found: C, 49.15; H, 5.91; N, 3.47.

Ethyl 3-carboethoxy-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxy-butanoate, 18d. Ethyl 3-carboethoxy-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxy-butanoate, **15d**, (0.42 g, 1.0 mmol) was dissolved in tetrahydrofuran

(40 mL) and cooled to 0 °C. Sodium triacetoxymethylborohydride (0.25 g, 1.2 mmol) was added, and the reaction mixture was allowed to stir for 18 h at room temperature. Ethyl acetate (40 mL) was added, and the reaction mixture was washed with water (3 x 40 mL) and with brine (1 x 40 mL). The aqueous layers were washed with ethyl acetate, and the combined organic layers were dried over MgSO₄, passed over a pad of silica gel, and evaporated to give a clear oil (0.34 g, 81 %). Roughly a 2:3 ratio of the two sets of diastereomers was obtained. Decomposition prevented the separation of the diastereomers.: ¹H NMR (400 MHz, CDCl₃) δ 1.16 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.27 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.331 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.335 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.97 (s, 3H, CH₃), 1.99 (s, 3H, CH₃), 3.45 (br s, 1H, CHOH), 4.17 (q, 2H, J=7.2, OCH₂), 4.27 (q, 2H, J=7.2, OCH₂), 4.30 (q, 2H, J=7.2, OCH₂), 4.31 (q, 2H, J=7.2, OCH₂), 4.44 (s, 1H, CHOH), 8.17 and 8.39 (AA'BB', J=8.8 Hz, 4H, aromatic CH), 8.18 and 8.38 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 13.9, 14.0, (14.0), (14.0), 19.3, 20.0, 62.75, 62.80, 62.9, 63.0, 74.6, 75.1, 90.8, 90.9, 124.17, 124.23, 128.9, 129.1, 143.8, 143.9, 150.5, 150.6, 167.7, 168.0, 169.6, 169.9; IR (neat) 3491, 3109, 2986, 1745, 1609, 1534, 1352, 1268, 1191, 1109, 1015, 916, 855, 745 cm⁻¹.

2-Carboethoxy-1-hydroxy-cyclohexene, 19. Ethyl 3-(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-3-cyclohexylpropionate, **15f**, (0.26g, 0.67 mmol) was dissolved in tetrahydrofuran (40 mL) and cooled to 0 °C. Sodium triacetoxymethylborohydride (0.16g, 0.75 mmol) was added, and the reaction was allowed to stir overnight at room temperature. Ethyl acetate (40 mL) was added, and the

organic layer was washed with water (3 x 25 mL) and with brine (1 x 25 mL). The combined aqueous layers were washed with ethyl acetate, dried over MgSO_4 , and evaporated to give a pale yellow oil (0.13g, >100%). The crude was purified by kugelrohr distillation and later by preparative tlc to afford enough sample for structure determination.: ^1H NMR (400 MHz, CDCl_3) δ 1.29 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.53-1.67 (m, 4H, CH_2CH_2), 1.75-1.80 (m, 1H, CH_2), 2.06-2.08 (m, 2H, CH_2), 2.15 (m, 1H, CH_2), 3.07 (d, $J=5.2$ Hz, 1H, CHOH), 4.25 (dq, $J=4.2$, $J=7.2$ Hz, 1H, OCHH), 4.27 (dq, $J=4.2$, $J=7.2$ Hz, 1H, OCHH), 4.47 (d, $J=5.2$ Hz, 1H, CHOH), 5.83 (br s, 1H, C=CH); ^{13}C NMR (400 MHz, CDCl_3) δ 14.2, 22.1, 22.4, 23.7, 25.1, 61.9, 75.4, 127.4, 134.9, 174.0; IR (neat) 3484, 2930, 2858, 1733, 1673, 1535, 1449, 1369, 1257, 1203, 1165, 1092, 1068, 1043, 1022 cm^{-1} .

Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-acetoxy-4-phenylbutanoate, 20b. Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxy-4-phenylbutanoate, **18b**, (0.30g, 0.73 mmol) was dissolved in methylene chloride (40 mL), and acetyl chloride (1.4 mL, 1.55 g, 19.7 mmol), pyridine (0.50 mL, 0.49 g, 6.2 mmol) and 4-dimethylaminopyridine (0.046g, 0.38 mmol) were added. The reaction was allowed to stir for 6 h at room temperature. The reaction was washed with dilute hydrochloric acid (1N, 1 x 40 mL), saturated bicarbonate (1 x 40 mL), and brine (1 x 40 mL). The combined aqueous layers were washed with methylene chloride (1 x 40 mL). The combined organic phases were dried over MgSO_4 , passed over a small pad of silica gel, and evaporated to yield an orange oil. Recrystallization from ethyl acetate/hexane afforded a yellow solid (0.31g, 94%): ^1H NMR (400 MHz,

CDCl₃) δ 1.26 (t, $J=7.2$ Hz, 3H, OCH₂CH₃), 2.23 (s, 3H, CH₃), 3.06 (d, $J=7.4$ Hz, 2H, Ph-CH₂), 4.12 (dq, $J=7.2$, $J=10.4$ Hz, 1H, OCHH), 4.16 (dq, $J=7.2$, $J=10.4$ Hz, 1H, OCHH), 5.13 (d, $J=2.8$ Hz, 1H, CH(OAc)), 5.40 (dt, $J=2.8$, $J=7.4$ Hz, 1H, CHONs), 7.04-7.07 (m, 2H, aromatic CH), 7.19-7.21 (m, 3H, aromatic CH), 7.81 and 8.22 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 13.9, 20.4, 37.5, 62.4, 71.8, 82.1, 124.2, 127.5, 128.91, 128.92, 129.3, 134.5, 142.0, 150.5, 166.5, 169.7; IR (KBr) 3113, 2987, 1757, 1737, 1611, 1534, 1380, 1351, 1313, 1275, 1227, 1184, 1097, 1029, 918, 855, 776, 740 cm⁻¹; Analysis calc'd for C₂₀H₂₁NO₉S: C, 53.21; H, 4.69; N, 3.10; found: C, 52.96; H, 4.45; N, 3.13.

Ethyl 3-carboethoxy-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-acetoxybutanoate, 20d. Ethyl 3-carboethoxy-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxybutanoate, **18d**, (0.25 g, 0.62 mmol) was dissolved in methylene chloride (40 mL), and acetyl chloride (0.50 mL, 0.55 g, 7.0 mmol), pyridine (0.10 mL, 0.098 g, 1.2 mmol), and DMAP (0.022 g, 0.2 mmol) were added. The reaction was allowed to stir for 4 h at room temperature. The reaction mixture was washed with dilute HCl (1 M, 1 x 40 mL), with saturated bicarbonate (1 x 40 mL), and with brine (1 x 40 mL). The combined aqueous layers were washed with methylene chloride (1 x 40 mL). The combined organic layers were dried over MgSO₄, passed over a small pad of silica gel, and evaporated to yield a clear oil (0.24 g, 86 %). The crude mixture consisted of two sets of diastereomers in a 1:1 ratio. The diastereomers were separated by HPLC (20.5 mL/min, hexane:ethyl acetate = 4:1). Two fractions (61 %) in a 52:48 ratio were collected. Compound at *t*_R 15.34 min (major,

0.09 g, 32 %).: ^1H NMR (400 MHz, CDCl_3) δ 1.25 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.32 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 2.01 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 4.20 (dq, 1H, $J=7.2$, $J=7.2$, OCHH), 4.21 (dq, 1H, $J=7.2$, $J=7.2$, OCHH), 4.29 (dq, 1H, $J=7.2$, $J=7.2$, OCHH), 4.30 (dq, 1H, $J=7.2$, $J=7.2$, OCHH), 5.34 (s, 1H, CHOAc), 8.16 and 8.40 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 13.9, (13.9), 19.3, 20.4, 62.5, 63.0, 75.2, 88.2, 124.2, 129.0, 143.6, 150.6, 164.9, 166.9, 169.4; IR (neat) 3109, 2986, 1756, 1609, 1537, 1373, 1353, 1192, 1086, 1020, 938, 854, 746 cm^{-1} ; Analysis calc'd for $\text{C}_{17}\text{H}_{21}\text{NO}_{11}\text{S}$: C, 45.64; H, 4.73; N, 3.13; found: C, 45.45; H, 4.77; N, 3.02.

Compound at t_R 16.92 min (minor, 0.08 g, 29 %).: ^1H NMR (400 MHz, CDCl_3) δ 1.15 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.33 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.97 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 4.12 (dq, 1H, $J=7.2$, $J=10.2$, OCHH), 4.16 (dq, 1H, $J=7.2$, $J=10.2$, OCHH), 4.31 (q, 2H, $J=7.2$, OCH_2), 5.37 (s, 1H, CHOAc), 8.18 and 8.38 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 13.9, 14.0, 20.1, 20.4, 62.3, 63.1, 74.6, 88.3, 124.1, 128.9, 143.9, 150.5, 165.1, 167.1, 169.4; IR (neat) 3109, 2985, 1759, 1609, 1535, 1373, 1352, 1264, 1213, 1192, 1088, 939, 855, 746 cm^{-1} ; Analysis calc'd for $\text{C}_{17}\text{H}_{21}\text{NO}_{11}\text{S}$: C, 45.64; H, 4.73; N, 3.13; found: C, 45.82; H, 4.69; N, 2.99.

***cis*-Ethyl 4-phenyl-2,3-oxiranebutanoate, 22b.** Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxy-4-phenylbutanoate, **18b**, (0.26g, 0.64 mmol) was dissolved in absolute ethanol (8 mL), and dry potassium carbonate (0.31 g, 2.26 mmol) was added. The reaction was allowed to stir for 24 h at room

temperature. Diethyl ether (45 mL) was added, and the organic layer was washed with water (40 mL). The layers were separated, and the aqueous phase was washed with ether (2 x 30 mL). The combined organic phases were washed with brine (25 mL), dried over MgSO_4 , and evaporated to dryness to afford a pale yellow oil (0.11 g, 85 %). The crude was purified by kugelrohr distillation to afford a pale yellow oil (0.10 g, 77 %).: ^1H NMR (400 MHz, CDCl_3) δ 1.32 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 2.90 (dd, $J=6.4$, $J=14.8$ Hz, 1H, Ph-CHH), 3.11 (dd, $J=6.0$, $J=14.8$ Hz, 1H, Ph-CHH), 3.39 (dt, $J=4.8$, $J=6.4$ Hz, 1H, $\text{C}(\text{O})\text{HCO}_2$), 3.57 (d, $J=4.8$ Hz, 1H, $\text{PhCH}_2\text{C}(\text{O})\text{H}$), 4.30 (q, $J=7.2$ Hz, 2H, OCH_2), 7.21-7.34 (m, 5H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 14.3, 33.8, 52.8, 57.7, 61.6, 126.9, 128.7, 128.9, 136.6, 168.3; IR (neat) 2983, 1749, 1605, 1497, 1455, 1380, 1255, 1091, 1198, 1032 cm^{-1} .

***cis*-Ethyl 2,3-oxirane octanoate, 22c.** Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-hydroxy-4-octanoate, **18c**, (0.20 g, 0.51 mmol) was dissolved in absolute ethanol (8 mL), and dry potassium carbonate (0.31 g, 2.2 mmol) was added. The reaction was allowed to stir for 24 h at room temperature. Diethyl ether (45 mL) was added, and the organic layer was washed with water (40 mL). The layers were separated, and the aqueous phase was washed with ether (2 x 30 mL). The combined organic phases were washed with brine (25 mL), dried over MgSO_4 , and evaporated to dryness to afford a pale yellow oil. The crude was separated using preparative tlc (ethyl acetate: hexane, 1:4) to afford a yellow oil (0.043 g, 45 %).: ^1H NMR (400 MHz, CDCl_3) δ 0.89 (t, $J=6.8$ Hz, 3H, $\text{CH}_2\text{-CH}_3$), 1.31 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.50-1.75 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 3.17 (dt, $J=4.8$, $J=5.8$ Hz, 1H,

CH₂CH(O)), 3.51 (d, J=4.8 Hz, 1H, CH(O)CO₂Et), 4.26 (dq, J=2.0, J=7.2 Hz, 2H, OCH₂); ¹³C NMR (400 MHz, CDCl₃) δ 13.9, 14.2, 22.5, 25.8, 27.2, 31.4, 62.9, 57.7, 61.4, 168.4; IR (neat) 2928, 2859, 1753, 1467, 1380, 1258, 1197, 1029, 912, 732 cm⁻¹.

Ethyl 2,3-dihydroxy octanoate, 23 This compound was isolated as a side product during the purification of ethyl 2,3-oxirane octanoate, **22c**, by preparative tlc. Evidently, the silica gel was wet, and the ring-opening occurred while the glycidic ester was on the silica gel.: ¹H NMR (400 MHz, CDCl₃) δ 0.90 (t, J=6.8 Hz, 3H, CH₂-CH₃), 1.32 (t, J=7.0 Hz, 3H, OCH₂CH₃), 1.38-1.60 (m, 8H, CH₂CH₂CH₂CH₂), 3.84-3.91 (m, 1H, CH₂CH(OH)), 4.09 (d, J=1.6, CH(OH)CO₂Et), 4.22 (d, J=3.6 Hz, 1H, CH(OH)CO₂Et), 4.30 (q, J=7.2 Hz, 2H, OCH₂); ¹³C NMR (400 MHz, CDCl₃) δ 14.0, (14.0), 14.17, 14.19, 22.5, 22.6, 25.38, 25.40, 31.7, 33.8, 62.0, 62.2, 72.5, 73.0, 73.2, 73.9, 172.8, 173.7; IR (neat) 3419, 2930, 2860, 1733, 1467, 1378, 1205, 1136, 1095 cm⁻¹.

Ethyl 3-morpholino-2-oxo-4-phenyl butanoate, 24. Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-4-phenylbutanoate, **15b**, (0.30 g, 0.74 mmol) was dried by toluene reflux. The solvent was evaporated, and the starting material was dissolved in acetonitrile (50 mL) and cooled to 0 °C. Morpholine (0.13 mL, 0.13 g, 1.5 mmol) was added, and the reaction mixture was allowed to stir for 4.5 h at 0 °C. Methylene chloride (50 mL) was added, and the organic layers were washed with cold water (2 x 25 mL) and with cold brine (1 x 25 mL). The combined aqueous extracts were combined and washed with methylene chloride (1 x 50 mL). The combined organic phases were dried

over MgSO_4 and evaporated to afford a yellow oil. The crude was dissolved in methylene chloride, filtered through cotton to remove the salt, and hexane was added until cloudy. A small additional amount of precipitate was collected, and the filtrate was evaporated to yield (0.17 g, 81 %) the desired product.: ^1H NMR (400 MHz, CDCl_3) δ 1.32 (t, $J=6.8$ Hz, 3H, CH_2CH_3), 2.62 (t, $J=4.2$ Hz, 4H, $\text{N}-(\text{CH}_2)_2$), 2.89 (dd, $J=5.6$, $J=13.8$ Hz, 1H, PhCHH), 3.05 (dd, $J=8.6$, $J=13.8$ Hz, 1H, PhCHH), 3.56-3.64 (m, 4H, $\text{O}-(\text{CH}_2)_2$), 4.16 (dd, $J=5.6$, $J=8.6$ Hz, 1H, CHN), 4.28 (q, $J=6.8$ Hz, 2H, OCH_2CH_3), 7.21-7.27 (m, 5H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 13.1, 28.6, 48.5, 61.0, 66.3, 68.7, 125.4, 127.6, 128.3, 137.1, 162.8, 190.6; IR (neat) 2962, 2854, 1744, 1728, 1604, 1455, 1262, 1117, 1070, 1024, 737, 701 cm^{-1} .

Ethyl 3-morpholino-2-hydroxy-4-phenyl butanoate, 25. Ethyl 3-morpholino-2-oxo-4-phenyl butanoate, **24**, (0.06 g, 0.21 mmol) was dissolved in a mixture (99:1) of tetrahydrofuran (37.8 mL) and methanol (0.4 mL). The solution was cooled to -78°C , and sodium borohydride (0.049 g, 1.3 mmol) was added. The reaction was allowed to stir for 30 minutes at -78°C . Water (50 mL) was added and the pH was adjusted to neutral. The aqueous layer was extracted with ethyl acetate (3 x 40 mL). The organic layers were combined, dried over MgSO_4 , evaporated to yield an off-white solid (0.70 g, >100%). Purification using preparative tlc (ethyl acetate: hexane, 2:3) was done. A clear oil (0.20 g, 33 %) was obtained.: ^1H NMR (400 MHz, CDCl_3) δ 1.26 (t, $J=7.2$ Hz, 3H, CH_2CH_3), 2.54-2.58 (m, 2H, $\text{N}-(\text{CH}_2)_2$), 2.83-2.88 (m, 2H, $\text{N}-(\text{CH}_2)_2$), 2.94-2.96 (m, 2H, PhCH_2), 3.03-3.08 (m, 1H, CHN), 3.62-3.63 (m, 4H, $\text{O}-(\text{CH}_2)_2$), 4.01 (d, $J=4.8$ Hz, 1H, CHOH), 4.12 (dq, $J=7.2$, $J=10.8$ Hz,

1H, OCHH), 4.22 (dq, J=7.2, J=10.8 Hz, 1H, OCHH), 7.21-7.30 (m, 5H, aromatic CH); ¹H NMR (400 MHz, acetone-d₆) δ 1.22 (t, J=7.2 Hz, 3H, CH₂CH₃), 2.51-2.56 (m, 2H, N-(CH₂)), 2.83 (br s, 2H, N-(CH₂)), 2.93-2.98 (m, 2H, PhCH₂), 3.05-3.09 (m, 1H, CHN), 3.53 (dt, J=3.6, J=5.6 Hz, 4H, O-(CH₂)₂), 4.02 (d, J=4.0 Hz, 1H, CHOH), 4.07 (dq, J=7.2, J=10.8 Hz, 1H, OCHH), 4.22 (dq, J=7.2, J=10.8 Hz, 1H, OCHH), 7.18-7.21 (m, 2H, aromatic CH), 7.27-7.34 (m, 3H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 13.3, 29.8, 49.7, 60.4, 66.5, 67.2, 71.2, 125.3, 127.5, 128.3, 138.2, 173.2; IR (neat) 3495, 2950, 2931, 2853, 1733, 1614, 1455, 1253, 1186, 1118, 1017, 923, 742, 701 cm⁻¹.

Reaction of Ethyl 3-carboethoxy-3-[(p-nitrobenzenesulfonyl)oxy]-2-oxo-butanoate, 15d, with DBU. Ethyl 3-carboethoxy-3-[(p-nitrobenzenesulfonyl)oxy]-2-oxo-butanoate, 15d, (0.24 g, 0.60 mmol) was dissolved in acetonitrile (50 mL) and cooled to 0 °C. DBU (0.09 mL, 0.0929g, 0.60 mmol) was added, and the reaction was allowed to stir for 5h at 0 °C. Methylene chloride (50 mL) was added, and the organic layer was washed with cold water (2 x 25 mL) and with brine (1 x 25 mL). The combined aqueous layers were washed with methylene chloride (1 x 25 mL). The combined organic layers were dried over MgSO₄ and evaporated to dryness to afford a pale yellow oil (0.14 g). A mixture of three products was obtained. Purification by radial chromatography was done (ethyl acetate: hexane, 1:4). The first fraction (0.049 g) contained ethyl 2-[(p-nitrobenzenesulfonyl)oxy] propanoate, **29** (27 %) and another unidentifiable compound.: ¹H NMR (400 MHz, CDCl₃) δ 1.23 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.60 (d, J=7.2 Hz, 3H, CH₃), 4.15 (q,

J=7.2 Hz, 2H, OCH₂), 5.10 (q, J=7.2 Hz, 1H, CHCH₃), 8.16 and 8.40 (AA'BB', J=8.8 Hz, 4H, aromatic CH); IR (neat) 3109, 2985, 1750, 1608, 1537, 1352, 1303, 1189 cm⁻¹; C₁₁H₁₃NO₇S. The third compound was identified as ethyl 2-hydroxy-2-(*p*-nitrophenyl)-propanoate, **28** (0.051 g, 36%): ¹H NMR (400 MHz, CDCl₃) δ 1.32 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.85 (s, 3H, CH₃), 4.04 (s, 1H, OH), 4.28 (dq, J=7.2, J=11.0 Hz, 1H, OCHH), 4.34 (dq, J=7.2, J=11.0 Hz, 1H, OCHH), 7.83 and 8.25 (AA'BB', J=8.8 Hz, 4H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 14.0, 27.2, 63.1, 75.5, 123.4, 126.6, 129.4, 149.8, 174.6; IR (neat) 3490, 2984, 1735, 1606, 1523, 1349, 1256, 856, 703 cm⁻¹.

Ethyl 3-azido-2-oxo-4-phenylbutanoate, 30b. Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-4-phenylbutanoate, **15b**, (0.39 g, 0.96 mmol) was dried by toluene reflux. After evaporation, **15b** was dissolved in dry acetone (30 mL), and sodium azide (0.124 g, 1.91 mmol) was added. The reaction was stirred for 7h at 0 °C. Water (50 mL) was added, and the aqueous layer was washed with ethyl acetate (3 x 50 mL). The combined organic layers were dried over MgSO₄ and evaporated to give a dark yellow oil (0.183 g, 77 %). Due to the instability of the product, no further purification was attempted.: ¹H NMR (400 MHz, CDCl₃) δ 1.37 (t, J=7.2 Hz, 3H, CH₃), 2.96 (dd, J=8.8, J=13.8 Hz, 1H, Ph-CHH), 3.23 (dd, J= 5.2, J=13.8 Hz, 1H, Ph-CHH), 4.33 (q, J=7.2 Hz, 2H, CH₂), 4.76 (dd, J=5.2, J=8.8 Hz, 1H, CHON₃), 7.25-7.34 (m, 5H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 13.9, 36.3, 63.2, 65.5, 127.4, 128.9, 129.3, 135.4, 160.4, 189.8; IR (neat) 2961, 2925, 2119, 1732, 1605, 1455, 1260, 1068, 1015, 700 cm⁻¹.

Ethyl 3-azido-2-hydroxy-4-phenylbutanoate, 31b. Sodium borohydride (0.093 g, 2.5 mmol) was slowly added to a cooled (-78 °C) solution of tetrahydrofuran:methanol (20 mL: 0.5 mL). Ethyl 3-azido-2-oxo-4-phenylbutanoate, **30b**, (0.21g, 0.85 mmol) in tetrahydrofuran (25 mL) was added, and the mixture was allowed to stir at -78 °C for 30 minutes. Water (50 mL) was added and the pH was adjusted to neutral. The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were dried over MgSO₄ and evaporated to give an opaque, yellow oil (0.19 g, 90%). The crude was dissolved in methylene chloride, leaving an insoluble, white solid. The filtrate was evaporated to give (0.17 g, 81%) of a yellow oil.: ¹H NMR (200 MHz, CDCl₃) δ 1.28 (t, J=7.2 Hz, 3H, CH₃), 3.12 (d, J=7.8 Hz, 2H, Ph-CH₂), 3.72-3.79 (m, 1H, CHN₃), 4.11 (d, J=2.0 Hz, 1H, CHOH), 4.25 (dq, J=3.6, J=7.2 Hz, 1H, OCHH), 4.29 (dq, J=3.6, J=7.2 Hz, 1H, OCHH), 7.24-7.39 (m, 5H, aromatic CH); ¹³C NMR (200 MHz, CDCl₃) δ 13.1, 35.2, 61.4, 63.3, 70.5, 126.0, 127.8, 128.4, 135.7, 171.7; IR (neat) 3446, 3236, 3030, 2982, 2933, 2112, 1739, 1604, 1496, 1455, 1259, 1115, 1023, 700 cm⁻¹.

***syn*-Ethyl 3-[(*p*-nitrobenzenesulfonyl)]oxy]-2-carboethoxy-4-phenylbutanoate, 33b.** *syn*-Ethyl 3-[(*p*-nitrobenzenesulfonyl)]oxy]-2-hydroxy-4-phenylbutanoate, **18b**, (0.17 g, 0.4 mmol) was dissolved in methylene chloride (25 mL), and ethyl chloroformate (1.0 mL, 1.14 g, 10.5 mmol), pyridine (0.06 mL, 0.59 g, 0.7 mmol), and DMAP (0.02 g, 0.2 mmol) were added. The reaction was allowed to stir for 24 h at room temperature. The organic layer was washed with water (3 x 25 mL), and the aqueous layer was

washed with methylene chloride (25 mL). The combined organic layers were dried over MgSO_4 and evaporated to yield a yellow oil (0.18 g, 90%).

Recrystallization from ethyl acetate/hexane afforded a white solid (0.10 g, 50%).: ^1H NMR (400 MHz, CDCl_3) δ 1.28 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.36 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 3.11 (d, $J=7.4$ Hz, 2H, PhCH_2), 4.17 (q, $J=7.2$ Hz, 2H, OCH_2), 4.27 (q, $J=7.2$ Hz, 2H, OCH_2), 4.99 (d, $J=2.6$ Hz, 1H, CHOCO_2Et), 5.40 (dt, $J=2.6$, $J=7.4$, 1, CHONs 7.09-7.11 (m, 2H, aromatic CH), 7.23-7.24 (m, 3H, aromatic CH), 7.85 and 8.24 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^1H NMR (400 MHz, acetone- d_6) δ 1.25 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 1.31 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 3.07 (dd, $J=7.8$, $J=14.0$ Hz, 1H, PhCHH), 3.16 (dd, $J=6.8$, $J=14.0$ Hz, 1H, PhCHH), 4.12 (dq, $J=7.2$, $J=11.0$ Hz, 1H, OCHH), 4.16 (dq, $J=7.2$, $J=11.0$ Hz, 1H, OCHH), 4.24 (q, $J=7.2$ Hz, 2H, OCH_2), 5.04 (d, $J=2.6$ Hz, 1H, CHOCO_2Et), 5.45 (ddd, $J=2.6$, $J=6.8$, $J=7.8$ Hz, 1H, CHONs), 7.14-7.22 (m, 5H, aromatic CH), 7.96 and 8.36 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 13.9, 14.2, 37.4, 62.5, 65.2, 74.3, 81.6, 124.2, 127.5, 128.96, 128.98, 129.4, 134.4, 142.0, 150.5, 154.0, 166.4; ^{13}C NMR (400 MHz, acetone- d_6) δ 14.2, 14.4, 37.9, 62.8, 65.6, 75.4, 83.1, 125.4, 128.0, 129.6, 129.9, 130.3, 135.8, 142.7, 151.7, 154.8, 167.0; IR (neat) 3109, 2985, 1754, 1608, 1534, 1375, 1351, 1312, 1255, 1187, 1096, 1026, 902, 745 cm^{-1} .

Ethyl 3-azido-2-carboethoxy-4-phenylbutanoate, 34b-SRP. Ethyl chloroformate (0.33 mL, 0.37 g, 3.5 mmol) and pyridine (0.075 mL, 0.073 g, 0.93 mmol), and DMAP (0.013 g, 0.11 mmol) were stirred in methylene chloride (15 mL) at 0 $^\circ\text{C}$ for 15 minutes. Ethyl 3-azido-2-hydroxy-4-

phenylbutanoate, **31b**, (0.17 g, 0.68 mmol) in methylene chloride (15 mL) was added, and the reaction was allowed to stir for 5 h at room temperature. The reaction was washed with water (2 x 30 mL), dried over MgSO₄, and passed over a small pad of silica gel. After evaporation, a yellow oil (0.17 g, 78 %) was collected. The crude was purified on preparative tlc using ethyl acetate: hexane: (2:3). A yellow oil (0.15 g, 68 %), that consists of two sets of diastereomers, *syn* and *anti* (76:24), was collected. **Syn-34b-SRP**: ¹H NMR (400 MHz, CDCl₃) δ 1.28 (t, J=7.2 Hz, 3H, OCH₂CH₃), 3.01 (dd, J=7.4, J=13.4 Hz, 1H, Ph-CHH), 3.08 (dd, J=8.0, J=13.4 Hz, 1H, Ph-CHH), 4.02 (dt, J=2.8, J=7.4 Hz, 1H, CHON₃), 4.16-4.31 (m, 2H, OCH₂), 4.89 (d, J=2.8 Hz, 1H, CHOCO₂Et), 7.21-7.35 (m, 5H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 14.1, 14.2, 36.4, 62.2, 62.6, 65.0, 75.5, 127.4, 129.0, 129.1, 135.9, 154.3, 167.5; IR (neat) 2964, 2931, 2856, 2115, 1751, 1604, 1456, 1374, 1256, 1095, 1024, 736, 701 cm⁻¹.

Anti-34b-SRP: ¹H NMR (400 MHz, CDCl₃) δ 1.37 (t, J=7.2 Hz, 3H, OCH₂CH₃), 2.99 (d, J=7.4 Hz, 2H, Ph-CH₂), 4.02 (dt, J=2.8, J=7.4 Hz, 1H, CHON₃), 4.16-4.31 (m, 2H, OCH₂), 5.10 (d, J=3.2 Hz, 1H, CHOCO₂Et), 7.21-7.35 (m, 5H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 14.1, 14.2, 36.0, 62.1, 63.2, 65.0, 76.4, 127.1, 128.7, 129.3, 136.3, 154.1, 166.9.

Anti-Ethyl 3-azido-2-carboethoxy-4-phenyl butyrate, anti-34b-RPS. *syn*-Ethyl 3-[(*p*-nitrobenzenesulfonyl)]oxy-2-carboethoxy-4-phenylbutanoate, **syn-33b**, (0.32 g, 0.66 mmol) was dissolved in dimethylsulfoxide (25 mL), and sodium azide (0.11 g, 1.7 mmol) was added. The reaction was refluxed at 60 °C overnight. Methylene chloride (50 mL) was added, and the organic layer

was washed with water (3 x 30 mL), and the combined aqueous layers were washed with methylene chloride (30 mL). The combined organic layers were dried over MgSO_4 and evaporated to yield a yellow oil (>100%). A mixture composed of **anti-34b-RPS** (47 %), the eliminated product, **35** (41 %), and the enol derivative, **36** (12 %) was determined by ^1H NMR. The yellow oil was separated using radial chromatography. A stepped, non-polar to polar, solvent system (ethyl acetate: hexane, 2:3 \rightarrow ethyl acetate) afforded a yellow oil (0.15 g). Although the products are easily discernible by ^1H NMR, a good separation of the three products was not achieved. Total yields of individual compounds in the purified mixture were **anti-34b-RPS** (29 %), **35** (36 %), **36** (12 %). Since the three compounds were never completely separated, only the partial assignment of the spectral data could be done.

anti-34b-RPS: ^1H NMR (400 MHz, CDCl_3) δ 3.00 (d, $J=7.4$ Hz, 2H, PhCH_2), 4.04 (dt, $J=3.2, 7.4$ Hz, 1H, CHN_3), 5.10 (d, $J=3.2$ Hz, 1H, CHOCO_2Et); ^{13}C NMR (400 MHz, CDCl_3) δ 36.0, 62.2, 63.2, 65.0, 76.4; IR for mixture: (neat) 2984, 2120, 1751, 1373, 1026 cm^{-1} ; $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_5$. IR (neat) 2984, 2120, 1751, 1373, 1026 cm^{-1} .

Ethyl 2-carboethoxy-3-ene-4-phenyl butyrate, 35: ^1H NMR (400 MHz, CDCl_3) δ 5.53 (d, $J=6.8$ Hz, 1H, CHOCO_2Et), 6.26 (dd, $J=6.8, J=16.0$ Hz, 1H, PhHC=CH), 6.85 (d, $J=16.0$ Hz, 1H, PhHC=CH).

Ethyl 2-carboethoxy-2-ene-4-phenyl butyrate, 36: ^1H NMR (400 MHz, CDCl_3) δ 3.56 (d, $J=7.6$ Hz, 2H, PhCH_2), 6.67 (t, $J=7.6$ Hz, 1H, PhCH_2CH).

Methyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-acetamido acrylate, 38.
Methyl 2-acetamido acrylate, **37**, (0.146 g, 1.0 mmol) was added to a solution of *p*-NPSP (0.404 g, 1.00 mmol) in ethyl acetate (50 mL), and the solution was cooled to 0 °C. The mixture was allowed to stir for 4h at 0 °C. After 4h, the reaction mixture was washed with sodium bicarbonate (1 x 25 mL), with brine (1 x 25 mL), dried over MgSO_4 , and evaporated to about 10 mL. Hexane was added until cloudy, and the solution was evaporated to dryness to afford a white solid. The crude solid was recrystallized from ethyl acetate/hexane, and a white solid (0.037 g, 11 %) was obtained. : m.p. 149-151°; ^1H NMR (400 MHz, CDCl_3) δ 2.07 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.70 (br s, 1H, NH), 7.59 (s, 1H, CH), 8.23 and 8.45 (AA'BB', $J=8.8$ Hz, 4H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 23.2, 52.9, 115.0, 124.6, 129.8, 138.0, 140.6, 151.3, 163.7, 167.4; IR (KBr) 3437, 3257, 3108, 1732, 1676, 1537, 1507, 1390, 1189, 1082, 819, 708 cm^{-1} .

4-Carboethoxy-5-benzyl-2-[3H] oxazolone, 40. Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-4-phenylbutanoate, **15b**, (0.31 g, 0.76 mmol) was dried by toluene (75 mL) reflux. Methyl carbamate (0.73 g, 9.7 mmol) and *p*-toluenesulfonic acid monohydrate (0.013g, 0.07 mmol) were added, and the reaction mixture was allowed to reflux for 48 h. The reaction mixture was allowed to cool to RT, and ethyl acetate (50 mL) was added. The organic

phase was washed with water (2 x 30 mL), with brine (1 x 30 mL), dried over MgSO_4 and evaporated to yield a dark orange oil. Purification by radial chromatography (ethyl acetate: hexane, 1:4) was done. The first fraction was methyl 4-nitrobenzene sulfonate, **39**, (0.14 g, 67 %) as confirmed by a pure sample obtained from Aldrich. A white solid (0.11 g, 58 %) was also obtained.: m.p. 141-142°; ^1H NMR (400 MHz, CDCl_3) δ 1.38 (t, $J=7.2$ Hz, 3H, CH_3), 4.11 (s, 2H, PhCH_2), 4.37 (q, $J=7.2$ Hz, 2H, OCH_2), 7.25-7.34 (m, 5H, aromatic CH), 8.32 (br s, 1H, NH); ^1H NMR (400 MHz, acetone- d_6) δ 1.35 (t, $J=7.2$ Hz, 3H, CH_3), 4.16 (s, 2H, PhCH_2), 4.36 (q, $J=7.2$ Hz, 2H, OCH_2), 7.25-7.34 (m, 5H, aromatic CH), 9.95 (br s, 1H, NH); ^{13}C NMR (400 MHz, CDCl_3) δ 14.2, 32.0, 61.8, 114.3, 127.3, 128.82, 128.84, 135.3, 148.1, 153.4, 158.8; ^{13}C NMR (400 MHz, acetone- d_6) δ 14.4, 32.3, 62.0, 115.6, 127.9, 129.5, 129.6, 137.2, 148.3, 153.9, 159.7; IR (KBr) 3440, 1762, 1718, 1670, 1314, 1172, 1053, 958, 795, 705 cm^{-1} ; Analysis calc'd for $\text{C}_{13}\text{H}_{13}\text{NO}_4$: C, 63.15; H, 5.30; N, 5.66; found: C, 62.91; H, 5.12; N, 5.31.

2-Methyl-4-carboethoxy-5-benzyl oxazole, 42. Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-4-phenylbutanoate, **15b**, (0.35 g, 0.86 mmol) was dried by toluene (75 mL) reflux. Acetamide (0.10 g, 1.7 mmol) and *p*-toluene-sulfonic acid (0.013g, 0.07 mmol) were added, and the reaction mixture was allowed to reflux for 4 h. The reaction mixture was allowed to cool to RT, and ethyl acetate (50 mL) was added. The organic phase was washed with water (2 x 40 mL), with brine (1 x 40 mL), dried over MgSO_4 and evaporated to yield a dark orange oil. Separation by radial chromatography (ethyl acetate: hexane, 1:4) afforded a clear oil (0.17 g, 80%): ^1H NMR (400 MHz, CDCl_3) δ

1.40 (t, $J=7.2$ Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.34 (s, 2H, PhCH_2), 4.40 (q, $J=7.2$ Hz, 2H, OCH_2), 7.22-7.30 (m, 5H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 13.8, 14.4, 32.0, 61.0, 127.0, 127.5, 128.7, 128.8, 136.4, 157.5, 160.2, 162.3; IR (neat) 3030, 2981, 2930, 1735, 1707, 1617, 1608, 1495, 1455, 1375, 1346, 1216, 1177, 1078, 854, 731, 703 cm^{-1} ; Analysis calc'd for $\text{C}_{14}\text{H}_{15}\text{NO}_3$: C, 68.56; H, 6.16; N, 5.71; found: C, 68.33; H, 5.97; N, 5.57.

2-Methyl-2-hydroxy-4-carboethoxy-5-benzyl-3-oxazoline, 46. Ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-4-phenylbutanoate, **15b**, (0.34 g, 0.84 mmol) was dried by toluene (75 mL) reflux. Acetamide (0.06 g, 1.1 mmol) and *p*-toluenesulfonic acid (0.008 g, 0.04 mmol) were added, and the reaction mixture was heated at 85 C for 4 h. The reaction mixture was allowed to cool to RT, and ethyl acetate (50 mL) was added. The organic phase was washed with water (2 x 40 mL), with brine (1 x 40 mL), dried over MgSO_4 and evaporated to yield an orange oil (0.25 g). Separation by radial chromatography (ethyl acetate: hexane, 1:4) afforded a clear oil (0.14 g, 64%): ^1H NMR (400 MHz, CDCl_3) δ 1.34 (t, $J=7.2$ Hz, 3H, CH_3), 2.07 (s, 3H, CH_3), 3.05 (dd, $J=8.8$, 14.2 Hz, 1H, PhCH_2H), 3.23 (dd, $J=4.4$, 14.2 Hz, 1H, PhCH_2H), 4.30 (q, $J=7.2$ Hz, 2H, OCH_2), 5.78 (dd, $J=4.4$, 8.8 Hz, 1H, PhCH_2CHO), 7.23-7.33 (m, 5H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 13.9, 20.3, 36.3, 62.8, 76.2, 127.3, 128.7, 129.4, 135.4, 159.7, 170.3, 189.8; IR (neat) 3473, 3030, 2984, 2940, 1766, 1733, 1372, 1234, 1053, 1031, 701 cm^{-1} .

2-Methyl-4-carboethoxy-4-hydroxy-5-benzyl-2-oxazoline, 47. ^1H NMR (400 MHz, CDCl_3) δ 1.24 (t, $J=7.2$ Hz, 3H, CH_3), 2.08 (s, 3H, CH_3), 3.06

(dd, J=8.2, 14.6 Hz, 1H, PhCHH), 3.11 (dd, J=5.6, 14.6 Hz, 1H, PhCHH), 4.18-4.26 (m, 2H, OCH₂), 4.95 (dd, J=5.6, 8.2 Hz, 1H, CHO), 7.21-7.34 (m, 5H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 14.0, 14.5, 34.4, 63.0, 85.4, 95.7, 126.7, 128.5, 129.2, 137.3, 170.2, 171.6; IR (neat) 3471, 3192, 2980, 2934, 1735, 1654, 1497, 1455, 1390, 1371, 1254, 1196, 1065, 1029, 739, 700 cm⁻¹.

2-methyl-2-hydroxy-4-carboethoxy-5-benzylloxazolidine, 51. Crude 2-methyl-2-hydroxy-4-carboethoxy-5-benzyl-3-oxazoline, **46**, (0.228 g, 0.86 mmol) was dissolved in tetrahydrofuran (40 mL), and sodium triacetoxyborohydride (0.21 g, 0.10 mmol) was added. The reaction was allowed to stir at RT for 24 h. Ethyl acetate (50 mL) was added, and the organic layer was washed with water (2 x 40 mL). The combined aqueous layers were washed with ethyl acetate (40 mL), and the combined organic phases were washed with brine (1 x 40 mL), dried over MgSO₄, passed over a pad of silica gel, and evaporated to afford an orange oil (0.28 g). The crude mixture consisted of two sets of diastereomers in an approximately 2:3 ratio. The crude was purified by radial chromatography (ethyl acetate:hexane, 1:4 --> 3:2) and then by preparative thin layer chromatography (ethyl acetate:hexane, 1:4). Two fractions (0.16 g, 70 %) in a 71:29 ratio were collected. The major compound ran faster. **Major:** ¹H NMR (400 MHz, CDCl₃) δ 1.23 (t, J=7.2 Hz, 3H, CH₃), 1.99 (s, 3H, CH₃), 3.03 (dd, J=6.8, 13.0 Hz, 1H, PhCHH), 3.07 (dd, J=8.2, 12.8 Hz, 1H, PhCHH), 4.09 (d, J=6.0, CHN), 4.17 (dq, J=3.2, 7.2 Hz, 1H, OCHH), 4.20 (dq, J=3.2, 7.2 Hz, 1H, OCHH), 5.34 (m, 1H, CHOH), 7.19-7.32 (m, 5H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 14.1, 20.8, 36.5, 62.1,

70.2, 75.2, 84.2, 126.9, 128.6, 129.7, 136.4, 172.7; IR (neat) 3483, 3029, 2983, 2926, 1739, 1604, 1535, 1496, 1455, 1373, 1235, 1114, 1030, 940, 748, 701 cm^{-1} ; $\text{C}_{14}\text{H}_{19}\text{NO}_4$. **Minor:** ^1H NMR (400 MHz, CDCl_3) δ 1.27 (t, $J=7.2$ Hz, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.94 (dd, $J=6.6, 13.8$ Hz, 1H, PhCHH), 3.01 (dd, $J=7.6, 13.8$ Hz, 1H, PhCHH), 3.21 (d, $J=5.2$, CHN), 4.08 (dq, $J=7.2, 10.6$ Hz, 1H, OCHH), 4.17 (dq, $J=7.2, 10.6$ Hz, 1H, OCHH), 4.31 (m, CHN), 5.36 (dt, $J=3.2, 7.0$ Hz, 1H, CHOH), 7.22-7.30 (m, 5H, aromatic CH); ^{13}C NMR (400 MHz, CDCl_3) δ 14.1, 21.0, 35.5, 62.3, 71.2, 75.8, 84.2, 126.8, 128.4, 129.6, 136.4, 170.5; IR (neat) 3486, 3030, 2982, 2928, 1742, 1605, 1534, 1497, 1455, 1373, 1236, 1132, 1096, 1061, 1030, 947, 748, 701 cm^{-1} .

Ethyl 2-acetamido-3-oxo-4-phenylbutanoate, 53. 2-methyl-4-carboethoxy-5-benzyl oxazole, **42**, (0.08g, 0.33 mmol) was dissolved in absolute ethanol (3 mL) and concentrated hydrochloric acid (3 drops) was added. The reaction mixture was allowed to stir at 60-65 $^{\circ}\text{C}$ for 8 h. The reaction mixture was cooled, and water (25 mL) was added. The aqueous layer was washed with ethyl acetate (3 x 25 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried over MgSO_4 and evaporated to yield an orange oil (0.09 g). Approximately a 50% conversion had been achieved. The crude was dissolved in ethyl acetate and passed over a small pad of silica gel. The filtrate was evaporated, and the resulting slushy solid was recrystallized from ethyl acetate/hexane to afford white crystals (0.03 g, 68%-corrected for 50% conversion).: ^1H NMR (400 MHz, CDCl_3) δ 1.30 (t, $J=7.2$ Hz, 3H, CH_3), 2.05 (s, 3H, CH_3), 4.00 (d, $J=16.2$ Hz, 1H, PhCHH), 4.05 (d, $J=16.2$ Hz, 1H, PhCHH), 4.24 (q, $J=7.2$ Hz, 2H, OCH_2), 5.35 (d, $J=6.8$ Hz,

1H, CHN), 6.66 (d, J=5.6 Hz, 1H, NH), 7.21-7.23 (m, 2H, aromatic CH), 7.28-7.35 (m, 3H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 14.0, 22.7, 47.6, 62.0, 62.8, 127.5, 128.8, 129.7, 132.5, 166.1, 169.8, 198.9; IR (neat) 3323, 2994, 1750, 1723, 1658, 1529, 1498, 1376, 1348, 1216, 1169, 1049, 1020, 715 cm⁻¹.

Ethyl 2-acetamido-3-hydroxy-4-phenylbutanoate, 56. Sodium borohydride (0.011 g, 0.3 mmol) was added to a solution of tetrahydrofuran (10 mL) and methanol (0.05 mL) at -78 °C. The mixture was allowed to stir for 5 minutes. Ethyl 2-acetamido-3-oxo-4-phenylbutanoate, **53** (0.02 g, 0.08 mmol) in tetrahydrofuran (5 mL) was added, and the reaction mixture was allowed to stir for 30 minutes at -78 °C. The reaction was allowed to warm-up to RT, and water (25 mL) was added. The pH of the solution was adjusted to 5-6 with dropwise addition of hydrochloric acid (1 M). The aqueous solution was washed with ethyl acetate (3 x 25 mL), and the combined organic layers were washed with brine (1 x 25 mL), dried over MgSO₄, passed over a pad of silica gel, and evaporated to give a clear oil (0.02 g). **Major fraction:** ¹H NMR (400 MHz, CDCl₃) δ 1.29 (t, J=7.2 Hz, 3H, CH₃), 2.07 (s, 3H, CH₃), 2.81 (dd, J=5.6, 14.0 Hz, 1H, PhCHH), 2.85 (dd, J=7.6, 14.0 Hz, 1H, PhCHH), 4.13 (dq, J=7.2, 10.8 Hz, 1H, OCHH), 4.09-4.28 (m, 2H, OCHH and CHOH), 4.71 (dd, J=2.8, 6.8 Hz, 1H, CHN), 6.51 (d, J=6.0 Hz, 1H, NH), 7.20-7.35 (m, 5H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 14.1, 23.1, 39.9, 57.7, 62.0, 74.2, 126.8, 128.6, 129.4, 137.4, 169.9, 171.2; IR (neat) 3352, 3026, 2926, 2855, 1738, 1652, 1538, 1455, 1375, 1262, 1205, 1084, 1029, 701 cm⁻¹; C₁₄H₁₉NO₄. **Minor fraction:** ¹H NMR (400 MHz, CDCl₃) δ 1.27 (t, J=7.2 Hz,

3H, CH₃), 2.12 (s, 3H, CH₃), 2.72 (dd, J=9.4, 13.8 Hz, 1H, PhCH_HH), 2.88 (dd, J=4.4, 13.8 Hz, 1H, PhCH_HH), 4.09-4.28 (m, 2H, OCH₂), 4.36 (ddd, J=2.0, 4.4, 4.6 Hz, 1H, CHN), 4.74 (dd, J=1.6, 9.0 Hz, 1H, CHOH), 6.34 (d, J=9.0 Hz, 1H, NH), 7.20-7.35 (m, 5H, aromatic CH); ¹³C NMR (400 MHz, CDCl₃) δ 14.1, 23.2, 40.4, 55.7, 61.8, 72.8, 127.0, 128.8, 129.4, 137.2, 170.7, 171.0.

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